	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	79	integrin adj binding adj (motif or domain)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:31			0
2	BRS	L2	2588	rgd	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:31			0
3	BRS	L3	31	1 same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:32			0
4	BRS	L4	40	peptide same (1 or 3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:33			0
5	BRS	L5	4264	bone adj growth	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:33			0
6	BRS	L6	3	4 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:44			0
7	BRS	L7	3	1 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:44			0
8	BRS	L8	1	3 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:44			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
9	BRS	L9	12	2 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:59			0
10	BRS	L10	16263	mouthwash or toothpaste	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 12:59			0
11	BRS	L11	0	10 same (6 or 7 or 8 or 9)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:00			0
12	BRS	L12	7	kumagai adj yoshinari.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:00			0
13	BRS	L13	41	yoneda adj toshiyuki.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:01			0
14	BRS	L14	0	blacher adj russel adj wayne.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:02			0
15	BRS	L15	1	(12 or 13) and 4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:02			0
16	BRS	L16	1	(12 or 13) and 1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:03			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
17	BRS	L17	3	(12 or 13) and 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/21 13:03			0

=> d his

(FILE 'HOME' ENTERED AT 13:14:26 ON 21 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
13:15:15 ON 21 APR 2003
L1 418 S INTEGRIN (W) BINDING (W) (MOTIF OR DOMAIN)
L2 16469 S RGD
L3 184 S L1 (P) L2
L4 15559 S BONE GROWTH
L5 1 S L3 (P) L4
L6 13 S (L1 OR L2) (P) L4
L7 5 DUPLICATE REMOVE L6 (8 DUPLICATES REMOVED)
L8 14842 S TOOTHPASTE OR MOUTHWASH
L9 3 S (L7 OR L3) (P) L8
L10 3 DUPLICATE REMOVE L9 (0 DUPLICATES REMOVED)
L11 2 S L10 NOT (L5 OR L7)

=> log y

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FILE 'HOME' ENTERED AT 13:14:26 ON 21 APR 2003

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

FILE 'MEDLINE' ENTERED AT 13:15:15 ON 21 APR 2003

FILE 'CAPLUS' ENTERED AT 13:15:15 ON 21 APR 2003
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FILE 'BIOSIS' ENTERED AT 13:15:15 ON 21 APR 2003
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FILE 'EMBASE' ENTERED AT 13:15:15 ON 21 APR 2003
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COPYRIGHT (C) 2003 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 13:15:15 ON 21 APR 2003

=> s integrin (w) binding (w) (motif or domain)
L1          418 INTEGRIN (W) BINDING (W) (MOTIF OR DOMAIN)

=> s rgd
L2        16469 RGD

=> s l1 (p) l2
L3          184 L1 (P) L2

=> s bone growth
L4        15559 BONE GROWTH

=> s l3 (p) l4
L5            1 L3 (P) L4

=> d l5 1 ibib abs

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:142473  CAPLUS
DOCUMENT NUMBER:          136:189126
TITLE:                    Dental products comprising a bone growth-enhancing
                          peptide
INVENTOR(S):              Yoneda, Toshiyuki; Nomizu, Motoyoshi; Kumagai,
                          Yoshinari
PATENT ASSIGNEE(S):       Big Bear Bio Inc., USA
SOURCE:                   PCT Int. Appl., 44 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2002013775      A1   20020221       WO 2001-US25101  20010809
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
             UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2001083268      A5   2001[redacted]25       AU 2001-83268    2001[redacted]09
```

PRIORITY APPLN. INFO.: US 2000-225879P P 20000816
WO 2001-US25101 W 20010809

AB Dental products such as toothpastes, mouthwash and dental floss are disclosed which products are enhanced by having dissolved, dispersed or coated thereon a compd. which promotes ***bone*** ***growth*** . Preferred compds. are peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. an ***integrin*** - ***binding*** ***motif*** such as ***RGD*** sequence and the remainder of amino acids contiguous with the ***RGD*** sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for dispersal in toothpaste or a mouthwash and administered to enhance bone/tooth growth. When the dental products are used repeatedly over time they enhance good dental health.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 13:14:26 ON 21 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 13:15:15 ON 21 APR 2003

L1 418 S INTEGRIN (W) BINDING (W) (MOTIF OR DOMAIN)
L2 16469 S RGD
L3 184 S L1 (P) L2
L4 15559 S BONE GROWTH
L5 1 S L3 (P) L4

=> s (l1 or l2) (p) l4
L6 13 (L1 OR L2) (P) L4

=> duplicate remove l6
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L6
L7 5 DUPLICATE REMOVE L6 (8 DUPLICATES REMOVED)

=> d l7 1-5 ibib abs

L7 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:142473 CAPLUS
DOCUMENT NUMBER: 136:189126
TITLE: Dental products comprising a bone growth-enhancing peptide
INVENTOR(S): Yoneda, Toshiyuki; Nomizu, Motoyoshi; Kumagai, Yoshinari
PATENT ASSIGNEE(S): Big Bear Bio Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002013775	A1	20020221	WO 2001-US25101	20010809
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001083268	A5	20020225	AU 2001-83268	20010809

PRIORITY APPLN. INFO.: US 2000-225879P P 20000816
WO 2001-US25101 W 20010809

AB Dental products such as toothpastes, mouthwash and dental floss are disclosed which products are enhanced by having dissolved, dispersed or

coated thereon a compd. which promotes ***bone*** ***growth*** . Preferred compds. are peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. an ***integrin*** - ***binding*** ***motif*** such as ***RGD*** sequence and the remainder of amino acids contiguous with the ***RGD*** sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for dispersal in toothpaste or a mouthwash and administered to enhance bone/tooth growth. When the dental products are used repeatedly over time they enhance good dental health.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002475694 MEDLINE
DOCUMENT NUMBER: 22223030 PubMed ID: 12218178
TITLE: Engineering growing tissues.
AUTHOR: Alsberg Eben; Anderson Kenneth W; Albeiruti Amru; Rowley Jon A; Mooney David J
CORPORATE SOURCE: Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109, USA.
CONTRACT NUMBER: GM08353 (NIGMS)
R01-DE13033 (NIDCR)
T32-DC05356 (NIDCD)
T32-DE07057 (NIDCR)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Sep 17) 99 (19) 12025-30. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020919
Last Updated on STN: 20030105
Entered Medline: 20021028
AB Regenerating or engineering new tissues and organs may one day allow routine replacement of lost or failing tissues and organs. However, these engineered tissues must not only grow to fill a defect and integrate with the host tissue, but often they must also grow in concert with the changing needs of the body over time. We hypothesized that tissues capable of growing with time could be engineered by supplying growth stimulus signals to cells from the biomaterial used for cell transplantation. In this study, chondrocytes and osteoblasts were cotransplanted on hydrogels modified with an ***RGD*** -containing peptide sequence to promote cell multiplication. New bone tissue was formed that grew in mass and cellularity by endochondral ossification in a manner similar to normal long- ***bone*** ***growth*** . Transplanted cells organized into structures that morphologically and functionally resembled growth plates. These engineered tissues could find utility in treating diseases and injuries of the growth plate, testing the effect of experimental drugs on growth-plate function and development, and investigating the biology of long- ***bone*** ***growth*** . Furthermore, this concept of promoting the growth of engineered tissues could find great utility in engineering numerous tissue types by way of the transplantation of a small number of precursor cells.

L7 ANSWER 3 OF 5 MEDLINE
ACCESSION NUMBER: 2002736837 MEDLINE
DOCUMENT NUMBER: 22387255 PubMed ID: 12499240
TITLE: The fate of the terminally differentiated chondrocyte: evidence for microenvironmental regulation of chondrocyte apoptosis.
AUTHOR: Adams Christopher S; Shapiro Irving M
CORPORATE SOURCE: Department of Orthopaedic Surgery, Thomas Jefferson Medical College, 1015 Walnut Street, 501, Philadelphia, PA 19107, USA.. Christopher.Adams@mail.tju.edu
CONTRACT NUMBER: DE-05748 (NIDCR)
DE-10875 (NIDCR)
DE-13319 (NIDCR)
SOURCE: CRITICAL REVIEWS IN ORAL BIOLOGY AND MEDICINE, (2002) 13 (6) 465-73. Ref: 72
Journal cod[redacted]9009999. ISSN: 1045-4411.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021227
Last Updated on STN: 20030331
Entered Medline: 20030328

AB Chondrocytes contained within the epiphyseal growth plate promote rapid ***bone*** ***growth*** . To achieve growth, cells activate a maturation program that results in an increase in chondrocyte number and volume and elaboration of a mineralized matrix; subsequently, the matrix is resorbed and the terminally differentiated cells are deleted from the bone. The major objective of this review is to examine the fate of the epiphyseal chondrocytes in the growing bone. Current studies strongly suggest that the terminally differentiated epiphyseal cells are deleted from the cartilage by apoptosis. Indeed, morphological, biochemical, and end-labeling techniques confirm that death is through the apoptotic pathway. Since the induction of apoptosis is spatially and temporally linked to the removal of the cartilage matrix, current studies have examined the apoptogenic activity of Ca(2+)-, Pi-, and ***RGD*** -containing peptides of extracellular matrix proteins. It is observed that all of these molecules are powerful apoptogens. With respect to the molecular mechanism of apoptosis, studies of cell death with Pi as an apoptogen indicate that the anion is transported into the cytosol via a Na(+/)Pi transporter. Subsequently, there is activation of caspases, generation of NO, and a decrease in the thiol reserve. Finally, we examine the notion that chondrocytes transdifferentiate into osteoblasts, and briefly review evidence for, and the rationale of, the transdifferentiation process. It is concluded that specific microenvironments exist in cartilage that can serve to direct chondrocyte apoptosis.

L7 ANSWER 4 OF 5 MEDLINE
ACCESSION NUMBER: 95056538 MEDLINE
DOCUMENT NUMBER: 95056538 PubMed ID: 7967062
TITLE: Biochemistry of bone matrix.
AUTHOR: Otawara-Hamamoto Y
CORPORATE SOURCE: Hoechst Japan Limited, Pharma Research & Development Division.
SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1994 Sep) 52 (9) 2239-45. Ref: 25
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941206

AB Bone matrix proteins can be divided into several groups according to their function; structural proteins, cell adhesive molecules, growth factors, proteinases and others. 1) Type I collagen is a major structural protein. 2) Osteopontin and bone sialoprotein (BSP) are ***RGD*** -containing cell adhesive proteins. Cadherins, OSF-2 and MGP also act as cell adhesive molecules in cell to cell or cell to matrix signal transition systems. 3) BMPs, TGF-b, IGFs, FGFs and PDGF are ***bone*** ***growth*** factors associated to bone matrix. 4) Collagenases and cathepsins are well known organic bone matrix degrading enzymes.

L7 ANSWER 5 OF 5 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 94189316 MEDLINE
DOCUMENT NUMBER: 94189316 PubMed ID: 8140932
TITLE: Synthetic peptide containing Arg-Gly-Asp inhibits bone formation and resorption in a mineralizing organ culture system of f[redacted]l rat parietal bones.
AUTHOR: Gronowicz G[redacted] Derome M E

CORPORATE SOURCE: Department of Orthopaedics, University of Connecticut Health Center, Farmington.
CONTRACT NUMBER: AR38636 (NIAMS)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1994 Feb) 9 (2) 193-201.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940509
Last Updated on STN: 19940509
Entered Medline: 19940426

AB The role of integrins, cell surface receptors involved in cell adhesion to the matrix, was studied in a mineralizing organ culture system. Integrin-mediated cell attachment to matrix proteins has been shown to depend partially on the amino acid sequence Arg-Gly-Asp (***RGD***), present in the extracellular matrix proteins. Therefore, the effect of ***RGD*** peptides on bone formation and resorption was studied in the mineralizing organ culture system derived from 18 day fetal rat parietal bones. Addition of 0.1-50 microM GRGDSPK to bones cultured for 4 days inhibited mineralization in a dose-dependent manner as determined by measuring calcium content and % bone/unit area of tissue. A maximal decrease in calcium content and % bone/unit area of 32.5 and 42.9%, respectively, was found with 50 microM GRGDSPK. With 10 and 50 microM GRGDSPK, bone morphology was dramatically altered, with a disruption of osteoblast and mineralized matrix organization. To assess the effect of the peptides on bone resorption, fetal bones were prelabeled in vivo with 45Ca and resorption was stimulated in vitro with parathyroid hormone in the presence or absence of the peptide. A significant decrease in 45Ca release was found with 10 and 50 microM GRGDSPK. Osteoclast number was also significantly decreased on the bone surface. The peptide was not cytotoxic, since no effect on DNA content, dry weight, or collagen synthesis was found. GRADSP, a control peptide, had no significant effect on mineralization, resorption, or other parameters of ***bone*** ***growth*** .(ABSTRACT TRUNCATED AT 250 WORDS)

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     (FILE 'HOME' ENTERED AT 13:14:26 ON 21 APR 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     13:15:15 ON 21 APR 2003
L1          418 S INTEGRIN (W) BINDING (W) (MOTIF OR DOMAIN)
L2        16469 S RGD
L3          184 S L1 (P) L2
L4        15559 S BONE GROWTH
L5            1 S L3 (P) L4
L6           13 S (L1 OR L2) (P) L4
L7            5 DUPLICATE REMOVE L6 (8 DUPLICATES REMOVED)

=> s toothpaste or mouthwash
L8       14842 TOOTHPASTE OR MOUTHWASH

=> s (l7 or l3) (p) l8
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L17) (P) L46'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L18) (P) L47'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L19) (P) L48'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L20) (P) L49'
L9            3 (L7 OR L3) (P) L8

=> duplicate remove l9
PROCESSING COMPLETED FOR L9
L10           3 DUPLICATE REMOVE L9 (0 DUPLICATES REMOVED)

=> s l10 not (l5 or l7)
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L11 2 L10 NOT (L5 OR L7)

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L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:978333 CAPLUS
DOCUMENT NUMBER: 138:33382
TITLE: Integrin binding motif containing peptides and methods of treating skeletal diseases
INVENTOR(S): Kumagai, Yoshinari; Yoneda, Toshiyuki; Blacher, Russell Wayne
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 641,034.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002197267	A1	20021226	US 2001-812485	20010319
WO 2002014360	A1	20020221	WO 2001-US25542	20010814

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001086491	A5	20020225	AU 2001-86491	20010814

PRIORITY APPLN. INFO.:
US 2000-641034 A2 20000816
US 2001-812485 A 20010319
WO 2001-US25542 W 20010814

AB Peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. at least one of an ***integrin*** - ***binding*** ***motif*** such as an ***RGD*** sequence, a glycosaminoglycan binding motif, and a calcium binding motif, and the remainder of amino acids contiguous with the ***RGD*** sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for injection or dispersed in ***toothpaste*** or a ***mouthwash*** or gum patch and administered to enhance bone/tooth growth and/or reduce excessive urinary phosphate loss from the body.

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:142748 CAPLUS
DOCUMENT NUMBER: 136:205385
TITLE: Integrin binding motif containing peptides and methods of treating skeletal diseases
INVENTOR(S): Kumagai, Yoshinari; Blacher, Russell Wayne; Yoneda, Toshiyunki
PATENT ASSIGNEE(S): Big Bear Bio Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014360	A1	20020221	WO 2001-US25542	20010814

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002197267 A1 20021226 US 2001-812485 20010319
AU 2001086491 A5 20020225 AU 2001-86491 20010814
PRIORITY APPLN. INFO.: US 2000-641034 A 20000816
US 2001-812485 A 20010319
WO 2001-US25542 W 20010814
OTHER SOURCE(S): MARPAT 136:205385
AB Peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. at least one of an ***integrin*** ***binding*** ***motif*** such as an ***RGD*** sequence, a glycosaminoglycan binding motif, and a calcium binding motif, and the remainder of amino acids contiguous with the ***RGD*** sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for injection or dispersed in ***toothpaste*** or a ***mouthwash*** or gum patch and administered to enhance bone/tooth growth and/or reduce excessive urinary phosphate loss from the body.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 13:14:26 ON 21 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 13:15:15 ON 21 APR 2003
L1 418 S INTEGRIN (W) BINDING (W) (MOTIF OR DOMAIN)
L2 16469 S RGD
L3 184 S L1 (P) L2
L4 15559 S BONE GROWTH
L5 1 S L3 (P) L4
L6 13 S (L1 OR L2) (P) L4
L7 5 DUPLICATE REMOVE L6 (8 DUPLICATES REMOVED)
L8 14842 S TOOTHPASTE OR MOUTHWASH
L9 3 S (L7 OR L3) (P) L8
L10 3 DUPLICATE REMOVE L9 (0 DUPLICATES REMOVED)
L11 2 S L10 NOT (L5 OR L7)

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	32.85	33.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.60	-2.60

STN INTERNATIONAL LOGOFF AT 13:20:47 ON 21 APR 2003

Kam 09/812,485

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=> d his 2

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     16:19:40 ON 21 APR 2003)
L26           3 S L25 AND TOOTHPASTE?
L27          71 S L25 NOT L26

=> d que l26
L1           31 SEA FILE=REGISTRY D.D.S.F.G..Q/SQSP
L2           16 SEA L1
L3            7 SEA L2 AND (INTEGRIN? OR GLYCOSAMINOGLYCAN# OR CALCIUM(3A)
                 BIND?)
L4           10 SEA L2 AND (BONE? OR OSTE?)
L5           11 SEA L3 OR L4
L6         1967 SEA KUMAGAI Y?/AU
L7         2646 SEA YONEDA T?/AU
L8          281 SEA BLACHER R?/AU
L9         4881 SEA (L6 OR L7 OR L8)
L10          64 SEA L9 AND (INTEGRIN? OR GLYCOSAMINOGLYCAN# OR CALCIUM(3A)
                 BIND?)
L11          23 SEA L10 AND (BONE? OR OSTE?)
L12          31 SEA L5 OR L11
L13       41884 SEA (BONE#(5A) GROWTH)
L14        9902 SEA INTEGRIN#(3A) BIND?
L15        2459 SEA GLYCOSAMINOGLYCAN#(3A) BIND?
L16       80252 SEA CALCIUM(3A) BIND?
L17       64432 SEA (BONE#(5A) RESOR?)
L18       48800 SEA OSTEOGEN?
L19         620 SEA (L13 OR L17 OR L18) AND ((L14 OR L15 OR L16))
L20         111 SEA L19 AND PEPTID?
L21         139 SEA L20 OR L12
L22         110 SEA L21 NOT PY>2000
L23          60 DUP REM L22 (50 DUPLICATES REMOVED)
L24          24 DUP REM L12 (7 DUPLICATES REMOVED)
L25          74 SEA L23 OR L24
L26           3 SEA L25 AND TOOTHPASTE?


=> d ibib abs l26 1-3

L26  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:978333  HCAPLUS
DOCUMENT NUMBER:          138:33382
TITLE:                    Integrin binding motif containing peptides
                          and methods of treating skeletal diseases
INVENTOR(S):              Kumagai, Yoshinari; Yoneda,
                          Toshiyuki; Blacher, Russell Wayne
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S.
                          Ser. No. 641,034.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     US 2002197267      A1   20021226      US 2001-812485   20010319
```

Search completed by David Schreiber 308-4292

WO 2002014360 A1 20020221 WO 2001-US25542 20010814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU 2001086491 A5 20020225 AU 2001-86491 20010814
PRIORITY APPLN. INFO.: US 2000-641034 A2 20000816
US 2001-812485 A 20010319
WO 2001-US25542 W 20010814

AB Peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. at least one of an **integrin** -binding motif such as an RGD sequence, a **glycosaminoglycan binding** motif, and a **calcium binding** motif, and the remainder of amino acids contiguous with the RGD sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for injection or dispersed in **toothpaste** or a mouthwash or gum patch and administered to enhance **bone**/tooth growth and/or reduce excessive urinary phosphate loss from the body.

L26 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:142748 HCAPLUS
DOCUMENT NUMBER: 136:205385
TITLE: **Integrin** binding motif containing peptides and methods of treating skeletal diseases
INVENTOR(S): **Kumagai, Yoshinari; Blacher, Russell Wayne; Yoneda, Toshiyunki**
PATENT ASSIGNEE(S): Big Bear Bio Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014360	A1	20020221	WO 2001-US25542	20010814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002197267	A1	20021226	US 2001-812485	20010319
AU 2001086491	A5	20020225	AU 2001-86491	20010814

PRIORITY APPLN. INFO.: US 2000-641034 A 20000816
US 2001-812485 A 20010319
WO 2001-US25542 W 20010814
OTHER SOURCE(S): MARPAT 136:205385

AB Peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. at least one of an **integrin**

binding motif such as an RGD sequence, a **glycosaminoglycan binding** motif, and a **calcium binding** motif, and the remainder of amino acids contiguous with the RGD sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for injection or dispersed in **toothpaste** or a mouthwash or gum patch and administered to enhance **bone**/tooth growth and/or reduce excessive urinary phosphate loss from the body.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:142473 HCAPLUS
DOCUMENT NUMBER: 136:189126
TITLE: Dental products comprising a **bone** growth-enhancing peptide
INVENTOR(S): **Yoneda, Toshiyuki**; Nomizu, Motoyoshi; **Kumagai, Yoshinari**
PATENT ASSIGNEE(S): Big Bear Bio Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002013775	A1	20020221	WO 2001-US25101	20010809
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001083268	A5	20020225	AU 2001-83268	20010809

PRIORITY APPLN. INFO.: US 2000-225879P P 20000816
WO 2001-US25101 W 20010809

AB Dental products such as **toothpastes**, mouthwash and dental floss are disclosed which products are enhanced by having dissolved, dispersed or coated thereon a compd. which promotes **bone** growth. Preferred compds. are peptide sequences comprising 10 to 50 amino acids are disclosed. The sequences are characterized by contg. an **integrin**-binding motif such as RGD sequence and the remainder of amino acids contiguous with the RGD sequence in matrix extracellular phosphoglycoprotein. The sequences may be formulated for dispersal in **toothpaste** or a mouthwash and administered to enhance **bone** /tooth growth. When the dental products are used repeatedly over time they enhance good dental health.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que l27
L1 31 SEA FILE=REGISTRY D.D.S.F.G..Q/SQSP
L2 16 SEA L1
L3 7 SEA L2 AND (INTEGRIN? OR GLYCOSAMINOGLYCAN# OR CALCIUM(3A)

Search completed by David Schreiber 308-4292

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                BIND?)
L4            10 SEA L2 AND (BONE? OR OSTE?)
L5            11 SEA L3 OR L4
L6          1967 SEA KUMAGAI Y?/AU
L7          2646 SEA YONEDA T?/AU
L8           281 SEA BLACHER R?/AU
L9          4881 SEA (L6 OR L7 OR L8)
L10           64 SEA L9 AND (INTEGRIN? OR GLYCOSAMINOGLYCAN# OR CALCIUM(3A)
                BIND?)
L11           23 SEA L10 AND (BONE? OR OSTE?)
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L13       41884 SEA (BONE#(5A) GROWTH)
L14        9902 SEA INTEGRIN#(3A) BIND?
L15        2459 SEA GLYCOSAMINOGLYCAN#(3A) BIND?
L16       80252 SEA CALCIUM(3A) BIND?
L17       64432 SEA (BONE#(5A) RESOR?)
L18       48800 SEA OSTEOGEN?
L19         620 SEA (L13 OR L17 OR L18) AND ((L14 OR L15 OR L16))
L20         111 SEA L19 AND PEPTID?
L21         139 SEA L20 OR L12
L22         110 SEA L21 NOT PY>2000
L23          60 DUP REM L22 (50 DUPLICATES REMOVED)
L24          24 DUP REM L12 (7 DUPLICATES REMOVED)
L25          74 SEA L23 OR L24
L26           3 SEA L25 AND TOOTHPASTE?
L27          71 SEA L25 NOT L26


=> d ibib abs l27 1-71

L27  ANSWER 1 OF 71     MEDLINE
ACCESSION NUMBER:    2001112841     MEDLINE
DOCUMENT NUMBER:     20583653   PubMed ID: 11150522
TITLE:               Matrix Gla protein is differentially expressed during the
                     deposition of a calcified matrix by vascular pericytes.
AUTHOR:              Canfield A E; Doherty M J; Kelly V; Newman B; Farrington C;
                     Grant M E; Boot-Handford R P
CORPORATE SOURCE:    Wellcome Trust Centre for Cell-Matrix Research, School of
                     Medicine, University of Manchester, Manchester, UK..
                     ann.canfield@man.ac.uk
SOURCE:              FEBS LETTERS, (2000 Dec 29) 487 (2) 267-71.
                     Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY:        Netherlands
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200102
ENTRY DATE:          Entered STN: 20010322
                     Last Updated on STN: 20010322
                     Entered Medline: 20010208
AB   PCR-based subtractive hybridisation was used to identify genes
     up-regulated when pericytes undergo osteogenic differentiation
     and deposit a calcified matrix. cDNA pools were generated from confluent
     pericytes and from pericyte cultures containing calcified nodules.  A
     pericyte cDNA library was screened with the product of the subtraction
     procedure (calcified minus confluent cDNA) and the majority of the
     positive clones were identified as matrix Gla protein (MGP).  Northern
     analysis and immunohistochemistry demonstrated that MGP was only expressed
     by pericytes in calcified nodules.  Antibodies to MGP inhibited the
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deposition of a calcified matrix by pericytes, suggesting that MGP regulates both cell differentiation and calcification.

L27 ANSWER 2 OF 71 MEDLINE
ACCESSION NUMBER: 2000492584 MEDLINE
DOCUMENT NUMBER: 20417777 PubMed ID: 10961900
TITLE: Cell-cell contact between marrow stromal cells and myeloma cells via VCAM-1 and alpha(4)beta(1)-**integrin** enhances production of **osteoclast**-stimulating activity.
AUTHOR: Michigami T; Shimizu N; Williams P J; Niewolna M; Dallas S L; Mundy G R; **Yoneda T**
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX 78284-7877, USA.
CONTRACT NUMBER: PO1-CA40035 (NCI)
R01-AR28149 (NIAMS)
RO1-DK45229 (NIDDK)
SOURCE: BLOOD, (2000 Sep 1) 96 (5) 1953-60.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001018

AB Myeloma is a unique hematologic malignancy that exclusively homes in the **bone** marrow and induces massive **osteoclastic** **bone** destruction presumably by producing cytokines that promote the differentiation of the hematopoietic progenitors to **osteoclasts** (**osteoclastogenesis**). It is recognized that neighboring **bone** marrow stromal cells influence the expression of the malignant phenotype in myeloma cells. This study examined the role of the interactions between myeloma cells and neighboring stromal cells in the production of **osteoclastogenic** factors to elucidate the mechanism underlying extensive **osteoclastic** **bone** destruction. A murine myeloma cell line 5TGM1, which causes severe **osteolysis**, expresses alpha(4)beta(1)-**integrin** and tightly adheres to the mouse marrow stromal cell line ST2, which expresses the vascular cell adhesion molecule-1 (VCAM-1), a ligand for alpha(4)beta(1)-**integrin**. Co-cultures of 5TGM1 with primary **bone** marrow cells generated tartrate-resistant acid phosphatase-positive multinucleated **bone**-resorbing **osteoclasts**. Co-cultures of 5TGM1 with ST2 showed increased production of **bone**-resorbing activity and neutralizing antibodies against VCAM-1 or alpha(4)beta(1)-**integrin** inhibited this. The 5TGM1 cells contacting recombinant VCAM-1 produced increased **osteoclastogenic** and **bone**-resorbing activity. The activity was not blocked by the neutralizing antibody to known **osteoclastogenic** cytokines including interleukin (IL)-1, IL-6, tumor necrosis factor, or parathyroid hormone-related peptide. These data suggest that myeloma cells are responsible for producing **osteoclastogenic** activity and that establishment of direct contact with marrow stromal cells via alpha(4)beta(1)-**integrin**/VCAM-1 increases the production of this activity by myeloma cells. They also suggest that the presence of stromal cells may provide a microenvironment that allows exclusive colonization of myeloma cells in the **bone**

marrow. (Blood. 2000;96:1953-1960)

L27 ANSWER 3 OF 71 MEDLINE
ACCESSION NUMBER: 2000455430 MEDLINE
DOCUMENT NUMBER: 20303091 PubMed ID: 10842093
TITLE: Integrins and signaling in osteoclast function.
AUTHOR: Duong L T; Lakkakorpi P; Nakamura I; Rodan G A
CORPORATE SOURCE: Department of Bone Biology and Osteoporosis, Merck Research Laboratories, West Point, PA 19486, USA.. duong@merck.com
SOURCE: MATRIX BIOLOGY, (2000 May) 19 (2) 97-105. Ref: 59
Journal code: 9432592. ISSN: 0945-053X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000926

AB Integrins are heterodimeric adhesion receptors that mediate cell-matrix and cell-cell interactions. Osteoclasts highly express the alphavbeta3 **integrin**, which **binds** to a variety of extracellular matrix proteins including vitronectin, osteopontin and bone sialoprotein. RGD-containing **peptides**, RGD-mimetics and alphavbeta3 blocking antibodies inhibit **bone resorption** in vitro and in vivo, suggesting that this integrin plays an important role in osteoclast function. RGD-containing **peptides** were shown to raise cytosolic calcium in osteoclasts. Furthermore, several signaling and adaptor molecules were found to be involved in alphavbeta3 integrin-dependent signaling pathways, including phosphatidylinositol 3-kinase, c-Src, PYK2 and p130(cas). In addition, cytoskeletal molecules such as paxillin, vinculin, gelsolin and F-actin are recruited to adhesion contacts upon integrin activation. Many of these molecules signaling and cytoskeletal localize to the sealing zone of actively resorbing osteoclasts, suggesting that they play a role in linking the adhesion of osteoclasts to the bone matrix with the cytoskeletal organization and the polarization and activation of these cells for **bone resorption**.

L27 ANSWER 4 OF 71 MEDLINE
ACCESSION NUMBER: 2000413850 MEDLINE
DOCUMENT NUMBER: 20291175 PubMed ID: 10828842
TITLE: **Peptidomimetic** antagonists of alphavbeta3 inhibit **bone resorption** by inhibiting osteoclast **bone resorptive** activity, not osteoclast adhesion to **bone**.
AUTHOR: Carron C P; Meyer D M; Engleman V W; Rico J G; Ruminski P G; Ornberg R L; Westlin W F; Nickols G A
CORPORATE SOURCE: Departments of Discovery Pharmacology, Medicinal Chemistry and Oncology, Searle Research and Development, Monsanto Company, St Louis, Missouri, 63198, USA.. chris.p.carron@monsanto.com
SOURCE: JOURNAL OF ENDOCRINOLOGY, (2000 Jun) 165 (3) 587-98.
Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

Search completed by David Schreiber 308-4292

ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000829

AB Osteoclasts are actively motile on bone surfaces and undergo alternating cycles of migration and resorption. Osteoclast interaction with the extracellular matrix plays a key role in the osteoclast resorptive process and a substantial body of evidence suggests that integrin receptors are important in osteoclast function. These **integrin** receptors **bind** to the Arg-Gly-Asp (RGD) sequence found in a variety of extracellular matrix proteins and it is well established that the interaction of osteoclast alpha v beta 3 integrin with the RGD motif within bone matrix proteins is important in osteoclast-mediated **bone resorption**. In this study, we characterized the effects of two synthetic **peptidomimetic** antagonists of alpha v beta 3, SC-56631 and SC-65811, on rabbit osteoclast adhesion to purified matrix proteins and **bone**, and on **bone resorption** in vitro. SC-56631 and SC-65811 are potent inhibitors of vitronectin binding to purified alpha v beta 3. Both SC-56631 and SC-65811 inhibited osteoclast adhesion to osteopontin- and vitronectin-coated surfaces and time-lapse video microscopy showed that osteoclasts rapidly retract from osteopontin-coated surfaces when exposed to SC-56631 and SC-65811. SC-56631 and SC-65811 blocked osteoclast-mediated **bone resorption** in a dose-responsive manner. Further analysis showed that SC-65811 and SC-56631 reduced the number of resorption pits produced per osteoclast and the average pit size. SC-65811 was a more potent inhibitor of **bone resorption** and the combination of reduced pit number and size led to a 90% inhibition of **bone resorption**. Surprisingly, however, osteoclasts treated with SC-65811, SC-56631 or the disintegrin echistatin, at concentrations that inhibit **bone resorption** did not inhibit osteoclast adhesion to bone. These results suggest that alphavbeta3 antagonists inhibited **bone resorption** by decreasing osteoclast **bone resorptive** activity or efficiency but not by inhibiting osteoclast adhesion to bone per se.

L27 ANSWER 5 OF 71 MEDLINE
ACCESSION NUMBER: 2000387119 MEDLINE
DOCUMENT NUMBER: 20347887 PubMed ID: 10779512
TITLE: Identification and purification of vitamin K-dependent proteins and **peptides** with monoclonal antibodies specific for gamma -carboxyglutamyl (Gla) residues.
AUTHOR: Brown M A; Stenberg L M; Persson U; Stenflo J
CORPORATE SOURCE: Department of Clinical Chemistry, Lund University, University Hospital, Malmo, S-205 02 Malmo, Sweden.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jun 30) 275 (26) 19795-802.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000810

AB Novel monoclonal antibodies that specifically recognize gamma-carboxyglutamyl (Gla) residues in proteins and **peptides**

Search completed by David Schreiber 308-4292

have been produced. As demonstrated by Western blot and time-resolved immunofluorescence assays the antibodies are pan-specific for most or all of the Gla-containing proteins tested (factors VII, IX, and X, prothrombin, protein C, protein S, **growth** arrest-specific protein 6, **bone** Gla protein, conantokin G from a cone snail, and factor Xa-like proteins from snake venom). Only the Gla-containing light chain of the two-chain proteins was bound. Decarboxylation destroyed the epitope(s) on prothrombin fragment 1, and Ca(2+) strongly inhibited binding to prothrombin. In Western blot, immunofluorescence, and surface plasmon resonance assays the antibodies bound **peptides** conjugated to bovine serum albumin that contained either a single Gla or a tandem pair of Gla residues. Binding was maintained when the sequence surrounding the Gla residue(s) was altered. Replacement of Gla with glutamic acid resulted in a complete loss of the epitope. The utility of the antibodies was demonstrated in immunochemical methods for detecting Gla-containing proteins and in the immunopurification of a factor Xa-like protein from tiger snake venom. The amino acid sequences of the Gla domain and portions of the heavy chain of the snake protein were determined.

L27 ANSWER 6 OF 71 MEDLINE
ACCESSION NUMBER: 2000131067 MEDLINE
DOCUMENT NUMBER: 20131067 PubMed ID: 10664443
TITLE: Cellular and molecular basis of preferential metastasis of breast cancer to **bone**.
AUTHOR: **Yoneda T**
CORPORATE SOURCE: Department of Biochemistry, Osaka University Faculty of Dentistry, 1-8 Yamada-oka, Suita, Osaka 565-0891, Japan.
SOURCE: JOURNAL OF ORTHOPAEDIC SCIENCE, (2000) 5 (1) 75-81. Ref: 48
Journal code: 9604934. ISSN: 0949-2658.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000215

AB **Bone** is one of the most preferential target sites for cancer metastasis. Breast cancer has a predilection for spreading to **bone**, and **bone** metastasis is one of the major causes of increased morbidity and eventual mortality in breast cancer patients. None of the currently available therapies is effective for curing **bone** metastases in these patients. Elucidation of the cellular and molecular mechanism by which breast cancer selectively spreads to **bone** is essential for the development of mechanism-based effective and specific therapeutic interventions for this deleterious complication in breast cancer. Here, two questions are addressed to study the mechanism of breast cancer metastasis to **bone**: (1) What makes **bone** a preferential target site of metastasis? (2) What makes breast cancer able to colonize **bone**? (3) An animal model in which intracardiac inoculation of breast cancer cells selectively causes **osteolytic bone** metastases was developed. Experimental results obtained using this unique in-vivo model of **bone** metastasis are described and discussed.

Search completed by David Schreiber 308-4292

L27 ANSWER 7 OF 71 MEDLINE
ACCESSION NUMBER: 2000080601 MEDLINE
DOCUMENT NUMBER: 20080601 PubMed ID: 10614938
TITLE: RGD-coated titanium implants stimulate increased bone formation in vivo.
AUTHOR: Ferris D M; Moodie G D; Dimond P M; Gioranni C W; Ehrlich M G; Valentini R F
CORPORATE SOURCE: Department of Molecular Pharmacology, Physiology, and Biotechnology, Brown University, Providence, RI 02912, USA.
SOURCE: BIOMATERIALS, (1999 Dec) 20 (23-24) 2323-31.
Journal code: 8100316. ISSN: 0142-9612.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000215

AB Numerous studies have demonstrated that **peptide** modified surfaces influence short- and long-term cell responses such as attachment, shape and function in vitro. These responses are mediated via cell receptors known as **integrins** which **bind** specifically to short **peptide** sequences from larger proteins. Integrins transduce information to the nucleus through several cytoplasmic signalling pathways. Little is known, however, about the ability of **peptide**-coated surfaces to influence cell responses in vivo. The present study was designed to evaluate the quality and quantity of the new bone formed in response to titanium rods surface-coated with the **peptide** sequence Arg-Gly-Asp-Cys (RGDC) using gold-thiol chemistry and implanted in rat femurs. Histomorphometric analysis of cross-sections perpendicular to the implant long axis showed a significantly thicker shell of new bone formed around RGD-modified versus plain implants at 2 weeks (26.2 +/- 1.9 vs. 20.5 +/- 2.9 microm; $P < 0.01$). A significant increase in bone thickness for RGD implants was also observed at 4 weeks while bone surrounding controls did not change significantly in thickness (32.7 +/- 4.6 vs. 22.6 +/- 4.0 microm; $P < 0.02$). Mechanical pull-out testing conducted at 4 weeks revealed the average interfacial shear strength of **peptide** modified rods was 38% greater than control rods although this difference was not statistically significant. These pilot data suggest that an RGDC **peptide** coating may enhance titanium rod osseointegration in the rat femur. Long-term studies and evaluation of other **peptides** in larger animal models are warranted.

L27 ANSWER 8 OF 71 MEDLINE
ACCESSION NUMBER: 1999454947 MEDLINE
DOCUMENT NUMBER: 99454947 PubMed ID: 10525079
TITLE: Design and characterization of orally active Arg-Gly-Asp **peptidomimetic** vitronectin receptor antagonist SB 265123 for prevention of bone loss in osteoporosis.
AUTHOR: Lark M W; Stroup G B; Hwang S M; James I E; Rieman D J; Drake F H; Bradbeer J N; Mathur A; Erhard K F; Newlander K A; Ross S T; Salyers K L; Smith B R; Miller W H; Huffman W F; Gowen M
CORPORATE SOURCE: Department of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania, USA.. michael__lark1@sbphrd.com
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,

(1999 Nov) 291 (2) 612-7.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124

AB The Arg-Gly-Asp (RGD)-**binding integrin** alpha(V)beta(3) is highly expressed on osteoclasts and has been proposed to mediate cell-matrix adhesion required for osteoclast-mediated **bone resorption**. Antagonism of this receptor should prevent stable osteoclast adhesion and thereby inhibit **bone resorption** . We have generated an orally bioavailable, nonpeptide RGD mimetic alpha(v)beta(3) antagonist, SB 265123, which prevents bone loss in vivo when dosed by oral administration. SB 265123 binds alpha(v)beta(3) and the closely related integrin alpha(v)beta(5) with high affinity (K(i) = 3.5 and 1.3 nM, respectively), but binds only weakly to the related RGD-**binding integrins** alpha(IIb)beta(3) (K(i) >1 microM) and alpha(5)beta(1) (K(i) >1 microM). The compound inhibits alpha(v)beta(3)-mediated cell adhesion with an IC(50) = 60 nM and more importantly, inhibits human osteoclast-mediated **bone resorption** in vitro with an IC(50) = 48 nM. In vivo, SB 265123 completely blocks **bone resorption** in a thyroparathyroidectomized rat model of acute **bone resorption** when dosed at 2.5 mg/kg/h by continuous i.v. infusion. When dosed orally with 3 to 30 mg/kg b.i.d. , in the ovariectomy-induced rat model of osteoporosis, SB 265123 prevents **bone resorption** in a dose-dependent fashion. This is the first report of an orally active alpha(v)beta(3) antagonist that is effective at inhibiting **bone resorption** when dosed in a pharmaceutically acceptable fashion. Such a molecule may provide a novel therapeutic agent for the treatment of postmenopausal osteoporosis.

L27 ANSWER 9 OF 71 MEDLINE

ACCESSION NUMBER: 1999099728 MEDLINE
DOCUMENT NUMBER: 99099728 PubMed ID: 9883275
TITLE: Nuclear and cytosolic calcium changes in osteoclasts stimulated with ATP and **integrin-binding peptide**.
AUTHOR: Parkinson N; Bolsover S; Mason W
CORPORATE SOURCE: Department of Physiology, University College London, UK.. nicola.parkinson@ucl.ac.uk
SOURCE: CELL CALCIUM, (1998 Sep) 24 (3) 213-21.
Journal code: 8006226. ISSN: 0143-4160.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 19990216
Entered Medline: 19990129

AB Cytosolic calcium modulates the activity of osteoclasts, large multinucleate cells that **resorb bone**. Nuclear events, such as gene transcription, are also calcium-regulated in these cells, and fluorescence imaging has suggested that calcium signals produced by some

stimuli are specifically targeted to, or amplified within, osteoclast nuclei. We used two alternative techniques of dye loading to examine the changes of intracellular calcium induced in rat osteoclasts by three stimuli. Osteoclasts loaded with the calcium indicator Fura-2 by the acetoxymethyl (AM) ester technique appeared to display marked nuclear calcium amplification. During stimulation with **integrin-binding peptides**, ATP, or high extracellular calcium, fluorescence ratios recorded from the nuclei rose higher than did ratios recorded from extranuclear regions. In contrast, nuclear calcium amplification was not observed after AM loading in the presence of the anion transport inhibitor sulfinpyrazone, nor in osteoclasts injected with Fura-2 conjugated to a high MW dextran. In these cells, nuclear fluorescence ratios were equal to the extranuclear values at all times: upon stimulation by an agonist, the nuclear and cytosolic calcium concentrations increased by the same amount. The calcium changes seen in stimulated osteoclasts can no longer be taken as evidence for the general validity of the phenomenon of nuclear calcium amplification.

L27 ANSWER 10 OF 71 MEDLINE
ACCESSION NUMBER: 1998184253 MEDLINE
DOCUMENT NUMBER: 98184253 PubMed ID: 9525341
TITLE: Contortrostatin, a homodimeric snake venom disintegrin, is a potent inhibitor of osteoclast attachment.
AUTHOR: Mercer B; Markland F; Minkin C
CORPORATE SOURCE: Department of Basic Sciences, School of Dentistry, University of Southern California, Los Angeles 90089-0641, USA.
CONTRACT NUMBER: AR40176 (NIAMS)
DE09965 (NIDCR)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1998 Mar) 13 (3) 409-14.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 20000303
Entered Medline: 19980610

AB Disintegrins are small disulfide-rich proteins containing an Arg-Gly-Asp (RGD) sequence near their carboxyl terminus. These polypeptides inhibit binding of adhesion molecules to their receptors (integrins) on the surface of cells. Osteoclasts express integrins, heterodimeric cell surface adhesion receptors, that have been shown to be involved in interactions with the extracellular matrix (ECM), including attachment to **bone** and **bone resorption**. It has recently been shown that disintegrins effectively inhibit attachment of osteoclasts to components of the ECM and also disrupt osteoclast-mediated **bone resorption**. Here we characterize the effects of contortrostatin (CTS), a novel homodimeric snake venom disintegrin, on osteoclast attachment. Plastic dishes coated with CTS were able to support osteoclast attachment with a high affinity (EC50,CTS = 86 +/- 6.7 nM) similar to that of vitronectin (VTN; EC50,VTN = 80 +/- 20 nM). Further, CTS was observed to inhibit completely osteoclast attachment to fetal bovine serum (FBS; IC50,FBS = 0.36 +/- 0.04 nM) and VTN (IC50,VTN = 0.85 +/- 0.13 nM). We used monoclonal antibodies directed against the beta1 (monoclonal antibody [MAb] CD29) and beta3 (MAb F11) integrin subunits to explore the mechanism of osteoclast attachment to immobilized CTS. Only

MAb F11 inhibited attachment to immobilized CTS (IC50 = 0.41 +/- 0.12 microg/ml), suggesting that binding to CTS is mediated in part by a beta3 integrin, presumably the alpha(v)beta3 VTN receptor. In further support of an **integrin**-mediated mechanism, **binding** of osteoclasts to CTS is inhibited by the RGD **peptide**, GRGDSP. CTS was also more potent (IC50,FBS = 0.36 +/- 0.04 nM) at inhibiting osteoclast attachment to FBS-coated wells than the monomeric snake venom disintegrin echistatin (IC50,FBS = 8.9 +/- 1.5 nM) or VTN (IC50FBS = 97.5 +/- 25.5 nM). Taken together, these data suggest that the snake venom disintegrin CTS is a potent inhibitor of beta3 integrin-mediated osteoclast attachment, presumably involving the VTN receptor (an alpha[v]beta3 integrin). Further studies of the mechanism of CTS-osteoclast interactions may aid in the design of **peptide** mimetics to act as antiresorptive agents for the treatment of osteoporosis and other skeletal pathology.

L27 ANSWER 11 OF 71 MEDLINE
ACCESSION NUMBER: 1998151042 MEDLINE
DOCUMENT NUMBER: 98151042 PubMed ID: 9492078
TITLE: The integrin ligand echistatin prevents bone loss in ovariectomized mice and rats.
AUTHOR: Yamamoto M; Fisher J E; Gentile M; Seedor J G; Leu C T; Rodan S B; Rodan G A
CORPORATE SOURCE: Department of Bone Biology and Osteoporosis Research, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.
SOURCE: ENDOCRINOLOGY, (1998 Mar) 139 (3) 1411-9.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 19980319
Entered Medline: 19980312

AB **Integrins** that **bind** RGD (arginine-glycine-aspartic acid) containing **peptides**, especially the vitronectin receptor alpha(v)beta3, have been implicated in the regulation of osteoclast function. Echistatin, an RGD-containing snake venom **peptide** with high affinity for beta3 integrins, as well as nonpeptide RGD mimetics, were shown to inhibit osteoclastic **bone resorption** in vitro and in vivo. To evaluate the role of RGD-**binding integrins** in bone metabolism, we examined by several methods the effects of echistatin on ovariectomy (OVX)-induced bone loss in mice and rats. First, we confirmed that echistatin binds in vitro with high affinity (Kd, 0.5 nM) to alpha(v)beta3 integrin purified from human placenta and established a competitive binding assay to measure echistatin concentrations in serum. We find that echistatin infused for 2 or 4 weeks at 0.36 microg/h x g body weight (approximately 50 nmol/day x mouse) completely prevents OVX-induced cancellous bone loss in the distal femora of ovariectomized mice. Echistatin has no effect on uterine weight, body weight, and femoral length changes induced by OVX, nor does it cause any apparent changes in major organs other than bone. In OVX rats, echistatin infusion at 0.26 microg/h x g for 4 weeks effectively prevents bone loss, evaluated by dual energy x-ray absorptiometry of the femur, by femoral ash weight, and by bone histomorphometry of the proximal tibia. At effective serum concentrations of 20-30 nM, measured at the end of the infusion period, echistatin maintains histomorphometric indices of bone turnover at control levels but does not decrease osteoclast surface.

In conclusion, these results provide in vivo evidence, at the level of bone histology, that RGD-**binding integrins**, probably alpha(v)beta3, play a rate-limiting role in osteoclastic **bone resorption** and suggest a therapeutic potential for integrin ligands in the suppression of bone loss.

L27 ANSWER 12 OF 71 MEDLINE
ACCESSION NUMBER: 97371214 MEDLINE
DOCUMENT NUMBER: 97371214 PubMed ID: 9227439
TITLE: **Osteogenic** protein-1 downregulates endothelin A receptors in primary rat osteoblasts.
AUTHOR: Kitten A M; Harvey S A; Criscimagna N; Asher M; Lee J C; Olson M S
CORPORATE SOURCE: Department of Biochemistry, University of Texas Health Science Center, San Antonio 78284-7760, USA.
CONTRACT NUMBER: DK-09195 (NIDDK)
DK-19473 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1997 Jun) 272 (6 Pt 1) E967-75.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 19970902
Entered Medline: 19970818

AB **Osteogenesis** is a complex process whereby growth factors and mediators from both local and systemic sources modulate the bone-forming activities of osteoblasts. In the present study we utilized primary cultures of fetal rat calvarial cells to characterize osteoblast responsiveness to the vascular mediator endothelin-1 (ET-1) and to investigate whether ET-1 responses are regulated by **osteogenic** protein-1 (OP-1). We found that a 1- to 2-day exposure to OP-1 diminished ET-1 receptor ligand binding and signal transduction by downregulating ET-1 receptor mRNA expression. ET-1-mediated **calcium** signaling and ligand **binding** were completely abolished by the ETA receptor antagonist BQ-123, suggesting that ET-1 effects are mediated by this receptor. Northern analysis of total RNA revealed that ETA mRNA expression was inhibited approximately 50% by OP-1 treatment, whereas ETB receptor mRNA was not detected by this method of analysis. In OP-1-treated cultures, the magnitude and duration of ET-1 calcium signals varied among individual cells. This finding may be related to a heterogeneous OP-1 response, indicated by alkaline phosphatase induction in only a subpopulation of cells. These results suggest that modulation of osteoblast function by ET-1 occurs during distinct periods of phenotypic development and imply that downregulation of ET-1 responsiveness may be necessary for optimal bone formation in vivo.

L27 ANSWER 13 OF 71 MEDLINE
ACCESSION NUMBER: 97136752 MEDLINE
DOCUMENT NUMBER: 97136752 PubMed ID: 8982129
TITLE: Response of human osteoblasts to implant materials: integrin-mediated adhesion.
AUTHOR: Gronowicz G; McCarthy M B
CORPORATE SOURCE: Department of Orthopaedics, University of Connecticut Health Center, Farmington 06030, USA..
gronowicz@nso1.uchc.edu

Search completed by David Schreiber 308-4292

CONTRACT NUMBER: AR43232 (NIAMS)
SOURCE: JOURNAL OF ORTHOPAEDIC RESEARCH, (1996 Nov) 14 (6) 878-87.
Journal code: 8404726. ISSN: 0736-0266.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19980206
Entered Medline: 19970127

AB The initial interaction of the human osteoblast-like cell line Saos-2 with orthopaedic implant materials was analyzed to determine the mechanism by which these cells adhere to implant surfaces. Saos-2 cells were allowed to attach to disks composed of the orthopaedic implant materials Tivanium (Ti6A14V) and Zimaloy (CoCrMo) and to control disks of glass and plastic. Serum had no effect on the number of cells that attached to Tivanium and Zimaloy at 4 or 24 hours but did increase the number of cells that attached to glass at 24 hours. Collagen synthesis was determined by [3H]proline incorporation into collagenase-digestible protein and noncollagen protein. A significant increase of 19% was found for collagen synthesized in cells cultured on Zimaloy for 24 hours compared with glass, with no differences on Tivanium and plastic. However, collagenase-digestible protein and noncollagen protein were increased the most (204 and 198%, respectively) on Tivanium compared with glass. To determine if integrins were involved in cell attachment to implant materials, the **peptide** GRGDSP (Gly-Arg-Gly-Asp-Ser-Pro), which blocks integrin receptors through the Arg-Gly-Asp sequence, was added to the cells in serum-free medium. This **peptide** inhibited cell adhesion by 28% on Tivanium and 40% on Zimaloy but had no effect on glass and plastic. The control **peptide** GRADSP (Gly-Arg-Ala-Asp-Ser-Pro) had no effect on adhesion. Inhibition of protein synthesis and enzymatic removal of surface proteins did not affect the ability of Arg-Gly-Asp **peptides** to inhibit cell attachment to the implant materials. These results suggest that **integrins** are able to **bind** directly to Tivanium and Zimaloy. Western blot analysis of integrin protein demonstrated changes in many integrin subunits, depending on the substrate to which cells attached. In particular, the beta 1 integrin subunit was increased 3.8 to 9.5-fold at 24 hours. To determine specifically which integrins may be involved in adhesion, antibodies to integrins were added. An antibody to the fibronectin receptor, alpha 5 beta 1, significantly inhibited binding of cells to Tivanium by 63% and to Zimaloy by 49% and had no effect on glass. The vitronectin receptor antibody, alpha v beta 3/beta 5, did not alter cell adhesion. In conclusion, osteoblast-like cells appear to be capable of attaching directly to implant materials through integrins. The type of substrate determines which integrins and extracellular matrix proteins are expressed by osteoblasts. These data provide information on how implant materials may affect osteoblast differentiation and **bone growth**.

L27 ANSWER 14 OF 71 MEDLINE
ACCESSION NUMBER: 97049407 MEDLINE
DOCUMENT NUMBER: 97049407 PubMed ID: 8894137
TITLE: Beta 1 integrins and osteoclast function: involvement in collagen recognition and **bone resorption**
.
AUTHOR: Helfrich M H; Nesbitt S A; Lakkakorpi P T; Barnes M J; Bodary S C; Shankar G; Mason W T; Mendrick D L; Vaananen H K; Horton M A

Search completed by David Schreiber 308-4292

CORPORATE SOURCE: Department of Medicine and Therapeutics, University of Aberdeen, Scotland.. m.helfrich@aberdeen.ac.uk
SOURCE: BONE, (1996 Oct) 19 (4) 317-28.
Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19970227
Entered Medline: 19970213

AB The extracellular matrix of bone is composed mainly of type I collagen. In this report we studied the role and collagen-**binding** properties of osteoclast **integrins** (alpha v, alpha 2, beta 1, and beta 3). Cell adhesion assays with rat osteoclasts and affinity chromatography/SDS-PAGE analysis with purified human osteoclast membranes demonstrated adhesion of osteoclasts to native type I collagen in a divalent cation and Arg-Gly-Asp (RGD)-dependent way via alpha 2 beta 1 integrin, whereas osteoclast adhesion to denatured collagen predominantly involved alpha v beta 3. In receptor-binding assays, the involvement of human recombinant alpha v beta 3 in adhesion to denatured collagen was confirmed. Additionally, osteoclasts adhered to type I collagen fibers and to monomeric types II-V collagen with characteristics similar to those on native monomeric type I collagen. Osteoclastic **bone resorption** in vitro was inhibited (> 40%) in the presence of alpha 2 and beta 1 antibodies. Using scanning laser confocal microscopy, alpha v beta 3, alpha 2, and beta 1 integrin were detected within podosomes in nonresorbing osteoclasts and in the ruffled border area and basolateral membrane in resorbing osteoclasts, but not in the sealing zone of resorbing osteoclasts. These results demonstrate that alpha 2 beta 1, in addition to alpha v beta 3, has an important role in osteoclast function and acts as a receptor for native, but not denatured, collagen.

L27 ANSWER 15 OF 71 MEDLINE
ACCESSION NUMBER: 97006132 MEDLINE
DOCUMENT NUMBER: 97006132 PubMed ID: 8853426
TITLE: Regulation of extracellular calcium sensing in rat osteoclasts by femtomolar calcitonin concentrations.
AUTHOR: Zaidi M; Shankar V S; Adebanjo O A; Lai F A; Pazianas M; Sunavala G; Spielman A I; Rifkin B R
CORPORATE SOURCE: Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, USA.
CONTRACT NUMBER: R01-DE-09576 (NIDCR)
R29-DE-10754 (NIDCR)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1996 Sep) 271 (3 Pt 2) F637-44.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19961205

AB Certain eukaryotic cells can sense changes in their extracellular Ca2+ concentration through molecular structures termed Ca(2+)-sensing receptors (CaRs). We have shown recently that in the **bone**-

resorbing osteoclast, a unique cell surface-expressed ryanodine receptor (RyR), functions as the CaR. The present study demonstrates that the sensitivity of this receptor is modulated by physiological femtomolar concentrations of the bone-conserving hormone, calcitonin. Calcitonin was found to inhibit cytosolic Ca2+ responses to both Ca2+ and Ni2+. The latter inhibition was mimicked by amylin (10(-12) M), calcitonin gene-related **peptide** (10(-12) M), cholera toxin (5 micrograms/l) and dibutyryl adenosine 3',5'-cyclic monophosphate (cAMP) (2.5 x 10(-4) or 5 x 10(-4) M) and was reversed by the protein kinase A phosphorylation inhibitor, IP-20. Finally, using a quench flow module, we showed that cellular cAMP levels rise to a peak within 25 ms of calcitonin application; this is consistent with the **peptide**'s rapid effect on CaR activation. We conclude, therefore, that cAMP plays a critical role in the control of CaR function by calcitonin.

L27 ANSWER 16 OF 71 MEDLINE
ACCESSION NUMBER: 95395365 MEDLINE
DOCUMENT NUMBER: 95395365 PubMed ID: 7665986
TITLE: Purification and characterization of the cytotoxic factor in rat peritoneal exudate cells: its identification as the **calcium binding** protein complex, calprotectin.
AUTHOR: Yui S; Mikami M; Yamazaki M
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Teikyo University, Kanagawa, Japan.
SOURCE: JOURNAL OF LEUKOCYTE BIOLOGY, (1995 Sep) 58 (3) 307-16. Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 19970203
Entered Medline: 19951006

AB We previously reported the existence of a growth inhibitory factor for mitogen-stimulated lymphocytes and murine tumor cell lines, MM46 and L-929, in inflammatory polymorphonuclear leukocytes. In this study, by using mouse MM46 mammary carcinoma as target, we purified the inhibitor from lysate of rat inflammatory peritoneal exudate cells by ammonium sulfate precipitation, gel filtration, isoelectrofocusing, and anion exchange chromatography. Although the in vitro inhibitory activity for MM46 growth was partitioned into three peaks in the final step, it was found that these inhibitory samples all consist of 8- and 13-kDa **peptides**. Analysis of amino acid sequences revealed that the partial sequences of the 8- and 13-kDa **peptides** completely agree with the smaller and larger components of rat calprotectin, which are predicted from cDNA, respectively, suggesting the cell growth inhibitory factor is calprotectin. In addition to MM46, the partially purified calprotectin inhibited the growth of a rat, three mice, and a human tumor cell line in similar dose-response relationships in vitro. Moreover, it exerted a cytolytic effect against all examined tumor cells. It was confirmed that the purified calprotectin induces growth inhibition and the lysis of MM46 cells and that the minimum effective concentration is between 50 and 100 micrograms/ml. The factor also inhibited the **growth** of **bone** marrow cells and macrophages. These results suggest that calprotectin is a negative regulatory factor for the growth and/or survival states of normal and tumor cells.

Search completed by David Schreiber 308-4292

L27 ANSWER 17 OF 71 MEDLINE
ACCESSION NUMBER: 95181558 MEDLINE
DOCUMENT NUMBER: 95181558 PubMed ID: 7876325
TITLE: Blockade of osteoclast-mediated **bone resorption** through occupancy of the integrin receptor: a potential approach to the therapy of osteoporosis.
AUTHOR: Dresner-Pollak R; Rosenblatt M
CORPORATE SOURCE: Thorndike Laboratory, Department of Medicine, Beth Israel Hospital, Boston, Massachusetts 02215.
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1994 Nov) 56 (3) 323-30. Ref: 29
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950419
Last Updated on STN: 19950419
Entered Medline: 19950331

AB **Bone resorption** requires the tight attachment of the **bone-resorbing** cells, the osteoclasts, to the **bone** mineralized matrix. Integrins, a class of cell surface adhesion glycoproteins, play a key role in the attachment process. Most **integrins bind** to their ligands via the arginyl-glycyl-aspartyl (R-G-D) tripeptide present within the ligand sequence. The interaction between integrins and ligands results in bidirectional transfer of signals across the plasma membrane. Tyrosine phosphorylation occurs within cells as a result of **integrin binding** to ligands and probably plays a role in the formation of the osteoclast clear zone, a specialized region of the osteoclast membrane maintained by cytoskeletal structure and involved in **bone resorption**. Human osteoclasts express alpha 2 beta 1 and alpha v beta 3 integrins on their surface. Such signaling may also lead to "inside-out" effects, like increased expression of integrin receptors on the cell surface, or increased affinity of the integrin to its ligand. The alpha v beta 3 integrin, a vitronectin receptor, plays an essential role in **bone resorption**. Antibodies to this integrin and short synthetic RGD-containing **peptides** are able to block **bone resorption** in vitro. Echistatin, an RGD-containing protein from a snake venom, binds to the alpha v beta 3 integrin and blocks **bone resorption** both in vitro and in vivo. **Peptides** containing the RGD motif are potential competitive "antagonists" of the osteoclast integrins and may have utility in the blockade of **bone resorption**. Agonists may be identified by stimulation of intracellular signaling.(ABSTRACT TRUNCATED AT 250 WORDS)

L27 ANSWER 18 OF 71 MEDLINE
ACCESSION NUMBER: 94249449 MEDLINE
DOCUMENT NUMBER: 94249449 PubMed ID: 8191932
TITLE: Effects of kistrin on **bone resorption** in vitro and serum calcium in vivo.
AUTHOR: King K L; D'Anza J J; Bodary S; Pitti R; Siegel M; Lazarus R A; Dennis M S; Hammonds R G Jr; Kukreja S C
CORPORATE SOURCE: Department of Cell Analysis, Genentech, Inc., South San

Francisco, California.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1994 Mar) 9 (3) 381-7.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940629
Last Updated on STN: 19940629
Entered Medline: 19940623

AB In many cell systems, cell-cell and cell-matrix interactions are mediated by integrins, a family of cell surface heterodimeric glycoprotein receptors. Osteoclast integrins may play a role in the process of **bone resorption**. Osteoclasts express the alpha v and beta 3 subunits of the vitronectin receptor and adhere to a wide range of proteins in vitro, all which contain the amino acid sequence Arg-Gly-Asp (RGD), an adhesion site recognition sequence common to many protein ligands that **bind** to **integrins**. The effect of kistrin, an RGD-containing snake venom protein, on osteoclast-mediated **bone resorption** was investigated in vivo and in vitro. When kistrin was infused into normocalcemic and hypercalcemic mice, serum calcium was significantly lowered at 3 and 6 h after the start of infusion, indicating an inhibitory effect on osteoclast activity in vivo. In vitro, kistrin potently inhibited **bone resorption** by isolated rat osteoclasts cultured on slices of bovine bone, and kistrin also inhibited the attachment of 293 cells expressing recombinant human alpha v beta 3 to fibrinogen (IC50 = 1 nM). These results indicate the potential therapeutic use of RGD-containing molecules for hypercalcemia of malignancy or for other disorders associated with bone loss.

L27 ANSWER 19 OF 71 MEDLINE
ACCESSION NUMBER: 94156892 MEDLINE
DOCUMENT NUMBER: 94156892 PubMed ID: 8113224
TITLE: **Calcium-binding** properties of osteopontin derived from non-**osteogenic** sources.
AUTHOR: Singh K; Deonarine D; Shanmugam V; Senger D R; Mukherjee A B; Chang P L; Prince C W; Mukherjee B B
CORPORATE SOURCE: Department of Biology, McGill University, Montreal, Quebec, Canada.
CONTRACT NUMBER: CA34025 (NCI)
DE00247 (NIDCR)
DE06739 (NIDCR)
SOURCE: JOURNAL OF BIOCHEMISTRY, (1993 Nov) 114 (5) 702-7.
Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940406
Last Updated on STN: 20000303
Entered Medline: 19940329

AB Osteopontin (OP), purified from rat bone, binds Ca2+ but whether different molecular forms of OPs derived from non-**osteogenic** sources and non-phosphorylated OP also possess this property remains to be determined. Furthermore, it is not known which specific site or sites of the molecule bind Ca2+. In the present study, following an established procedure,

total proteins in the conditioned media from OP-synthesizing cell cultures were separated by SDS-PAGE, transferred to Immobilon-P membranes, and incubated with 45CaCl2, then Ca2+ ions bound to protein bands were analyzed by autoradiography. Purified OPs, and synthetic oligopeptides representing specific domains of the OP molecule were adsorbed on the membrane and processed as described above. Our results show that OPs synthesized by normal rat kidney cells, oncogenically transformed Rat-1 cells, OP purified from human milk, and non-phosphorylated OP secreted by 1 alpha, 25-dihydroxyvitamin D3-treated mouse epidermal JB6 cells all bind detectable levels of Ca2+ with specificity. We also show that a synthetic **peptide** representing the domain of OP which contains nine consecutive aspartic acid residues binds Ca2+ with specificity. It is probable, therefore, that a Ca(2+)-binding site resides in this region of the OP molecule. We conclude that Ca(2+)-binding is a general property of OP, irrespective of its molecular mass and origin, and the phosphate moieties of OP may not influence the conformation or accessibility of the Ca2+ affinity sites of the molecule.

L27 ANSWER 20 OF 71 MEDLINE
ACCESSION NUMBER: 93366940 MEDLINE
DOCUMENT NUMBER: 93366940 PubMed ID: 7689577
TITLE: Integrin receptor-mediated mobilisation of intranuclear calcium in rat osteoclasts.
AUTHOR: Shankar G; Davison I; Helfrich M H; Mason W T; Horton M A
CORPORATE SOURCE: ICRF Haemopoiesis Research Group, St. Bartholomew's Hospital, London, UK.
SOURCE: JOURNAL OF CELL SCIENCE, (1993 May) 105 (Pt 1) 61-8. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931015
Last Updated on STN: 19960129
Entered Medline: 19930924

AB Cell-matrix interactions have been shown to play an important role in regulating cell function and behaviour. In **bone**, where calcified matrix formation and **resorption** events are required to be in dynamic equilibrium, regulation of adhesive interactions between bone cells and their matrix is critical. The present study focuses on the osteoclast, the **bone resorbing** cell, as well as integrins, which are cell surface adhesion receptors that mediate osteoclast attachment to bone matrix. In osteoclasts, the most abundant integrin receptor is the vitronectin receptor (VNR, alpha v beta 3). The objective of the study was to investigate changes in intracellular calcium, a regulator of osteoclast function, following addition of **peptides** that **bind integrins**, in particular the alpha v beta 3 form of the vitronectin receptor (VNR), which is highly expressed in osteoclasts. The study demonstrated a unique spatial localisation of the calcium signal in response to cell membrane receptor occupancy by integrin ligands in rat osteoclasts. Addition of **peptides** with the Arg-Gly-Asp (RGD) sequence such as BSP-IIA, GRGDSP and GRGDS to rat osteoclasts evoked an immediate increase in free calcium ion concentration [Ca2+]i, localised to the nuclei and to the thin cytoplasmic skirt. These responses were inhibited by F11, a monoclonal antibody to the rat integrin beta 3 chain, as well as echistatin, a snake venom shown to colocalise with the alpha v chain in osteoclasts, suggesting that the calcium signal is mediated by the alpha v beta 3 form

of VNR.(ABSTRACT TRUNCATED AT 250 WORDS)

L27 ANSWER 21 OF 71 MEDLINE
ACCESSION NUMBER: 93016627 MEDLINE
DOCUMENT NUMBER: 93016627 PubMed ID: 1400878
TITLE: Serum propeptide and intact molecular osteocalcin in normal children and children with growth hormone (GH) deficiency: a potential marker of **bone growth** and response to GH therapy.
AUTHOR: Kanzaki S; Hosoda K; Moriwake T; Tanaka H; Kubo T; Inoue M; Higuchi J; Yamaji T; Seino Y
CORPORATE SOURCE: Department of Pediatrics, Okayama University Medical School, Japan.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1992 Oct) 75 (4) 1104-9.
Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921113

AB To establish a sensitive marker for bone formation we have developed a sandwich enzyme-linked immunosorbent assay for intact osteocalcin (OC) and its propeptide. Serum levels of these **peptides** were studied in 185 normal children, aged 4-15 yr, and in 23 GH-deficient children treated with GH. The serum levels of the propeptide in normal prepubescent children were 1.43 +/- 0.23 (mean +/- SE) micrograms/L in boys and 1.53 +/- 0.23 micrograms/L in girls. The peak value occurred at the age of 13 yr in boys (2.91 +/- 0.42 micrograms/L) and 11 yr in girls (2.34 +/- 0.34 micrograms/L). The serum intact OC levels in prepubescent boys and girls were 18.8 +/- 2.1 and 20.7 +/- 2.1 micrograms/L, respectively, and these levels increased to 41.0 +/- 3.7 micrograms/L in boys aged 13 yr and to 27.0 +/- 2.5 micrograms/L in girls aged 11 yr. In the GH-deficient patients, a 2.3-fold increase in the propeptide level and a 1.7-fold increase in the intact OC level was observed after 1 month of GH therapy. Serum propeptide and intact OC levels after 1 month of GH therapy correlated with the growth response after 12 months of GH therapy ($r = 0.660$ and $P < 0.01$, for propeptide; $r = 0.537$ and $P < 0.01$ for intact OC). These results show that since both propeptide and intact OC in serum were increased when the growth rate was elevated, these **peptides** are sensitive markers of bone formation. Serum levels of these **peptides**, particularly propeptide, after 1 month of GH therapy might be a helpful predictor of the growth response to long term GH therapy.

L27 ANSWER 22 OF 71 MEDLINE
ACCESSION NUMBER: 91009504 MEDLINE
DOCUMENT NUMBER: 91009504 PubMed ID: 2211834
TITLE: Echistatin is a potent inhibitor of **bone resorption** in culture.
AUTHOR: Sato M; Sardana M K; Grasser W A; Garsky V M; Murray J M; Gould R J
CORPORATE SOURCE: Department of Bone Biology, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.
CONTRACT NUMBER: S10-RR05008 (NCRR)
SOURCE: JOURNAL OF CELL BIOLOGY, (1990 Oct) 111 (4) 1713-23.

Search completed by David Schreiber 308-4292

Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199011
ENTRY DATE: Entered STN: 19910117
Last Updated on STN: 19910117
Entered Medline: 19901102

AB The venom protein, s-echistatin, originally derived from the saw-scaled viper Echis carinatus, was found to be a potent inhibitor of **bone resorption** by isolated osteoclasts. This Arg24-Gly25-Asp26-(RGD)-containing protein inhibited the excavation of bone slices by rat osteoclasts (IC50 = 0.1 nM). It also inhibited the release of [3H]proline from labeled bone particles by chicken osteoclasts (IC50 = 100 nM). By comparison, the tetrapeptide Arg-Gly-Asp-Ser (RGDS) inhibited resorption by rat or chicken osteoclasts with an IC50 of 0.1 mM while ala24-echistatin was inactive. Video microscopy showed that rat osteoclast attachment to substrate was more sensitive to s-echistatin than was the attachment of mononuclear cells or chicken osteoclasts. The difference in sensitivity of rat and chicken osteoclasts to s-echistatin may be due to differences between receptors on rat and chicken osteoclasts for s-echistatin. Antibody localization of echistatin on these cells showed much greater echistatin binding to rat osteoclasts than to chicken osteoclasts. Laser scanning confocal microscopy after immunohistochemical staining showed that s-echistatin binds to osteoclasts, that s-echistatin receptors are most abundant at the osteoclast/glass interface, and that s-echistatin colocalizes with vinculin. Confocal interference reflection microscopy of osteoclasts incubated with s-echistatin, demonstrated colocalization of s-echistatin with the outer edges of clusters of grey contacts at the tips of some lamellipodia. Identification of the echistatin receptor as an integrin was confirmed by colocalization of echistatin fluorescence with staining for an alpha-like subunit. Attachment of bone particles labeled with [3H]proline to chicken osteoclasts confirmed that the mechanism of action of echistatin was to inhibit osteoclast binding to bone presumably by disrupting adhesion structures. These data demonstrate that osteoclasts bind to bone via an RGD-sequence as an obligatory step in **bone resorption**, that this RGD-**binding integrin** is at adhesion structures, and that it colocalizes with vinculin and has an alpha-like subunit.

L27 ANSWER 23 OF 71 MEDLINE
ACCESSION NUMBER: 90200403 MEDLINE
DOCUMENT NUMBER: 90200403 PubMed ID: 2630170
TITLE: Association of the C-propeptide of type II collagen with mineralization of embryonic chick long bone and sternal development.
AUTHOR: Kujawa M J; Weitzhandler M; Poole A R; Rosenberg L; Caplan A I
CORPORATE SOURCE: Biology Department, Case Western Reserve University, Cleveland, Ohio 44106.
SOURCE: CONNECTIVE TISSUE RESEARCH, (1989) 23 (2-3) 179-99.
Journal code: 0365263. ISSN: 0300-8207.
Report No.: NASA-90200403.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences

ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900509

AB Several proteins may play a role in bone formation. The C-propeptide of type II collagen is intimately associated with endochondral **bone** formation in bovine **growth** plate. We have used an antibody against this **peptide** to determine its immunofluorescent distribution in early stages of embryonic chick limb development with emphasis on first bone formation which occurs in the mid-diaphyseal region. The C-propeptide II is first evident by immunofluorescent localization at stage 27 (day 5-6) of embryonic tibia development with chondrocytes in the central mid-diaphysis. In subsequent stages, there is an increase in the number of chondrocytes in which it is localized in discrete vacuoles. Up to stage 30, immunofluorescence is observed intracellularly, after which it appears in the matrix. The released C-propeptide II appears to remain only transiently associated with the cartilage matrix and becomes concentrated in the calcifying periosteum, the region outside of the cartilage core where bone formation first occurs in a sequence of events comparable to intramembranous bone formation. These observations can be reproduced in cultures of stage 35 hypertrophic chondrocytes (core cells) and periosteum cells (collar cells). Core cells contain intensely stained intracellular vacuoles while collar cells are negative, although the collar cell **osteogenic** matrix concentrates exogenously added C-propeptide II. Double label immuno-staining shows that the C-propeptide II, unlike type II collagen and proteoglycan, which are secreted and incorporated into extracellular sites, is initially stored in intracellular vacuoles. The matrix localization of the C-propeptide II during the transition from cartilage to bone indicates a close association with the initiation of mineralization events of cartilage and bone and its specific origin in chondrocytes and not osteoblasts. These observations suggest that the C-propeptide II made by chondrocytes is associated with the formation of bone.

L27 ANSWER 24 OF 71 MEDLINE
ACCESSION NUMBER: 89340892 MEDLINE
DOCUMENT NUMBER: 89340892 PubMed ID: 2547836
TITLE: Human osteoblasts in vitro secrete tissue inhibitor of metalloproteinases and gelatinase but not interstitial collagenase as major cellular products.
AUTHOR: Rifas L; Halstead L R; Peck W A; Avioli L V; Welgus H G
CORPORATE SOURCE: Department of Medicine, Jewish Hospital, Washington University Medical Center, St. Louis, Missouri 63110.
CONTRACT NUMBER: AM-35805 (NIADDK)
AR-19855 (NIAMS)
AR-32087 (NIAMS)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1989 Aug) 84 (2) 686-94.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19890908

Search completed by David Schreiber 308-4292

AB Human osteoblast cultures (hOB) were examined for the production of interstitial collagenase, tissue inhibitor of metalloproteinases (TIMP), and gelatinolytic enzymes. Cells were isolated by bacterial collagenase digestion of trabecular bone (vertebra, rib, tibia, and femur) from 11 subjects (neonatal to adult). Confluent cultures were exposed to phorbol 12-myristate 13-acetate, PTH, PGE2, epidermal growth factor, 1,25(OH)2 vitamin D3, recombinant human IL-1 beta, and dexamethasone. Collagenase and TIMP were assayed immunologically and also by measurements of functional activity. Collagenase was not secreted in significant quantities by human bone cells under any tested condition. Furthermore, collagenase mRNA could not be detected in hOB. However, hOB spontaneously secreted large amounts of TIMP for at least 72 h in culture. hOB TIMP was found to be identical to human fibroblast TIMP by double immunodiffusion, metabolic labeling and immunoprecipitation, Northern blot analysis, and stoichiometry of collagenase inhibition. SDS-substrate gel electrophoresis of hOB-conditioned media revealed a prominent band of gelatinolytic activity at 68 kD, and specific polyclonal antisera established its identity with the major gelatinolytic protease of human fibroblasts. Abundant secretion of gelatinolytic, but not collagenolytic, enzymes by hOB may indicate that human osteoblasts do not initiate and direct the cleavage of osteoid collagen on the bone surface, but may participate in the preparation of the bone surface for osteoclast attachment by removal of denatured collagen **peptides**. The constitutive secretion of TIMP may function to regulate metalloproteinase activity.

L27 ANSWER 25 OF 71 MEDLINE
ACCESSION NUMBER: 89022290 MEDLINE
DOCUMENT NUMBER: 89022290 PubMed ID: 3509744
TITLE: Effect of acute increases in bone matrix degradation on circulating levels of bone-Gla protein.
AUTHOR: Riggs B L; Tsai K S; Mann K G
CORPORATE SOURCE: Division of Endocrinology and Metabolism and Internal Medicine, Mayo Clinic, Rochester, MN 55905.
CONTRACT NUMBER: AG-04875 (NIA)
AG-4876 (NIA)
MO1-RR00585 (NCRR)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1986 Dec) 1 (6) 539-42.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881114

AB Serum bone Gla-protein (BGP), also called osteocalcin, is a specific and sensitive measure of bone turnover in a variety of metabolic bone disorders. Although some BGP diffuses into the circulation after synthesis by osteoblasts, most is incorporated into bone matrix where it remains until **bone** is **resorbed**. Thus, serum BGP could reflect **bone** formation, **bone resorption**, or a combination of both. The relationship of serum BGP to the components of bone turnover was evaluated in 18 normal women (mean age 48 yr; range 30-70) who received a continuous 24-h intravenous infusion of the 1-34 synthetic fragment of bovine parathyroid hormone. Mean +/- SE for urinary hydroxyproline excretion, an index of **bone resorption**,

increased (from 22.7 +/- 2.2 to 38.5 +/- 3.7 micrograms/100 ml glomerular filtrate [GF], p less than .001), whereas levels of serum alkaline phosphatase, an index of bone formation, were unchanged (from 20 +/- 1 to 20 +/- 1 U/liter, NS). Despite the increase in **bone resorption**, levels of serum BGP decreased (from 8.8 +/- 0.8 to 6.8 ng/dl, p less than .001). The data suggest that circulating levels of BGP are a measure of bone formation but, at least in subjects with normal renal function, not a measure of **bone resorption**. Presumably BGP in **bone** matrix is degraded during osteoclastic **resorption** into fragments that either are not recognized by an antiserum raised against the native molecule or are rapidly cleared from the circulation.

L27 ANSWER 26 OF 71 MEDLINE
ACCESSION NUMBER: 88254696 MEDLINE
DOCUMENT NUMBER: 88254696 PubMed ID: 2838270
TITLE: Regulation of bovine **bone** cell proliferation by fibroblast **growth** factor and transforming growth factor beta.
AUTHOR: Globus R K; Patterson-Buckendahl P; Gospodarowicz D
CORPORATE SOURCE: Cancer Research Institute, University of California Medical Center, San Francisco 94143.
SOURCE: ENDOCRINOLOGY, (1988 Jul) 123 (1) 98-105.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880729

AB We have tested the hypothesis that basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF beta) regulate the proliferation of osteoblast-like cells. Cells which migrated from central bone explants of fetal calf calvaria expressed markers characteristic of the osteoblast phenotype, including osteocalcin (bone Gla protein) secretion and increased cAMP production in response to treatment with PTH. Bone cells proliferated in response to bFGF in a dose- and time-dependent pattern (ED50 = 60 pg/ml media). bFGF increased both the rate of bone cell proliferation (1.7-fold above controls) and final cell density at confluence (3-fold above controls). Acidic FGF (aFGF) exerted comparable effects though with lesser potency (ED50 = 2 ng/ml). In addition to its mitogenic effect, bFGF increased the osteocalcin content of conditioned media, suggesting that bFGF also modulates the function of osteoblast-like cells. Although TGF beta did not stimulate bone cell proliferation, it potentiated the mitogenic effects of aFGF and bFGF. In the presence of bFGF (0.7 ng/ml) the response to TGF beta was dose-dependent (ED50 = 1.7 ng/ml), with maximal stimulation at 5 ng/ml. These results demonstrate that aFGF and bFGF are mitogenic for bone cells in vitro. Furthermore, TGF beta potentiates the effects of bFGF and aFGF on the proliferation of bone cells. Since these **growth** factors are present in **bone** tissue in vivo, these data support the proposal that FGF and TGF beta may participate in the regulation of bone formation.

L27 ANSWER 27 OF 71 MEDLINE
ACCESSION NUMBER: 86217440 MEDLINE
DOCUMENT NUMBER: 86217440 PubMed ID: 3085902
TITLE: Human parathyroid hormone (1-34) and salmon calcitonin do

not reverse impaired mineralization produced by high doses of 1,25 dihydroxyvitamin D3.
AUTHOR: Gunness-Hey M; Hock J M; Gera I; Fonseca J; Poser J; Bevan J; Raisz L G
CONTRACT NUMBER: AM07030-02 (NIADDK)
AM18063 (NIADDK)
SOURCE: CALCIFIED TISSUE INTERNATIONAL, (1986 Apr) 38 (4) 234-8.
Journal code: 7905481. ISSN: 0171-967X.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860627

AB We have reported recently that pharmacologic doses of 1,25 dihydroxyvitamin D3 (1,25(OH)2D3) stimulated bone matrix formation but impaired mineralization. The objective of this study was to determine if parathyroid hormone (hPTH 1-34) or calcitonin (sCT) would mineralize the osteoid induced by 1,25(OH)2D3 in rat long bones. In one experiment, male Sprague-Dawley rats were given daily subcutaneous injections of vehicle: 8 micrograms hPTH(1-34); 125 ng 1,25(OH)2D3; or both 8 micrograms hPTH and 125 ng 1,25(OH)2D3 per 100 g body weight for 12 days. In a second experiment, rats received daily injections of vehicle: 2 U sCT; 125 ng 1,25(OH)2D3; or both 2 U sCT and 125 ng 1,25(OH)2D3 per 100 g body weight for 18 days. Calcium (Ca), hydroxyproline (Hyp), and dry weight (DW) of the distal femur and serum calcium, phosphate, and serum bone Gla protein (BGP) were measured. In rats given both 1,25(OH)2D3 and hPTH, total bone DW and Hyp increased (P less than .01) without a corresponding increase in bone Ca so that Ca/Hyp decreased 47% (P less than .01) from control and remained comparable to values for rats treated with 1,25(OH)2D3 alone. In rats treated with both 1,25(OH)2D3 and sCT, total bone DW and Hyp increased while Ca decreased so that Ca/Hyp decreased 38% from control (P less than .05), and remained comparable to values for rats treated with 1,25(OH)2D3 alone. These results indicate that hPTH or sCT, given by intermittent injection to rats for 12 or 18 days respectively, failed to mineralize the osteoid induced by high doses of 1,25(OH)2D3.

L27 ANSWER 28 OF 71 MEDLINE
ACCESSION NUMBER: 86189721 MEDLINE
DOCUMENT NUMBER: 86189721 PubMed ID: 2938732
TITLE: Bone metastases and breast cancer.
AUTHOR: Coleman R E; Rubens R D
SOURCE: CANCER TREATMENT REVIEWS, (1985 Dec) 12 (4) 251-70. Ref: 124
Journal code: 7502030. ISSN: 0305-7372.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860616

L27 ANSWER 29 OF 71 MEDLINE
ACCESSION NUMBER: 86081556 MEDLINE

Kam 09/812,485

DOCUMENT NUMBER: 86081556 PubMed ID: 3000756
TITLE: Local regulators of skeletal growth: a perspective.
AUTHOR: Centrella M; Canalis E
CONTRACT NUMBER: AM-21707 (NIADDK)
SOURCE: ENDOCRINE REVIEWS, (1985 Fall) 6 (4) 544-51. Ref: 52
Journal code: 8006258. ISSN: 0163-769X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 20000303
Entered Medline: 19860129

L27 ANSWER 30 OF 71 MEDLINE
ACCESSION NUMBER: 85125562 MEDLINE
DOCUMENT NUMBER: 85125562 PubMed ID: 3882294
TITLE: Effect of **growth** factors on **bone** cell replication and differentiation.
AUTHOR: Canalis E
CONTRACT NUMBER: AM21707 (NIADDK)
SOURCE: CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1985 Mar) (193) 246-63. Ref: 168
Journal code: 0075674. ISSN: 0009-921X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198504
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 20000303
Entered Medline: 19850410

AB Bone formation is a process regulated by effects on bone cell replication and on differentiated function, which is primarily represented by changes in bone collagen synthesis. The effects of hormones on bone formation have been reviewed extensively, and this article describes the effects of systemic and local growth factors. Systemic growth factors, such as epidermal growth factor and fibroblast growth factor, stimulate cell replication in skeletal and nonskeletal tissues but inhibit differentiated function; platelet-derived growth factor stimulates cell replication and generalized protein synthesis by differentiated cells. The only systemic factor that simultaneously stimulates bone cell replication and differentiation is insulinlike growth factor, or somatomedin. The growth of skeletal and nonskeletal tissues also appears to be regulated by locally synthesized factors. **Bone** contains an autologous **bone**-derived **growth** factor that stimulates **bone** collagen and DNA synthesis, while cartilage contains a somatomedinlike **peptide** that stimulates cartilage growth. Other noncollagenous bone proteins, such as osteonectin and osteocalcin, might have a role in mineralization, but, as yet, they have not been reported to have a definite effect on bone formation. Bone also contains prostaglandins and local regulators of **bone resorption**, while the macrophage, an osteoclast-related cell, releases **peptides** that stimulate bone formation in vitro. In conclusion, bone formation is a complex process regulated not only by hormones but also by systemic and local growth factors.

Search completed by David Schreiber 308-4292

L27 ANSWER 31 OF 71 MEDLINE
ACCESSION NUMBER: 85074232 MEDLINE
DOCUMENT NUMBER: 85074232 PubMed ID: 3917374
TITLE: Control of VX2 carcinoma cell growth in culture by calcium, calmodulin, and prostaglandins.
AUTHOR: **Yoneda T**; Kitamura M; Ogawa T; Aya S; Sakuda M
SOURCE: CANCER RESEARCH, (1985 Jan) 45 (1) 398-405.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198501
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850125

AB Based on our in vivo observation that growth of VX2 carcinoma transplanted in rabbits paralleled development of hypercalcemia, we studied the regulation of VX2 tumor growth using a clonal cell line isolated from VX2 tumor (VX2-L). VX2-L cell growth was dependent on prostaglandins released by the cultured cells into the medium, since indomethacin suppressed VX2-L growth, and prostaglandins A2, E1, E2, F1 alpha, and F2 alpha stimulated VX2-L proliferation. In contrast, prostaglandins D2 and I2 inhibited VX2-L proliferation. In contrast to previous reports, increases in extracellular calcium concentration promoted VX2-L growth not only directly but indirectly through augmentation of prostaglandin E synthesis. Antagonists of the intracellular **calcium binding** protein calmodulin inhibited cell replication. Increases in extracellular calcium also stimulated production of a nonprostaglandin macromolecular **bone**-resorbing factor. This factor may account for the hypercalcemia which we were unable to block by indomethacin. These results suggest a close relationship between VX2-L growth, prostaglandin production, and hypercalcemia. It is proposed that calcium blockers and anticalmodulin drugs might be powerful anticancer and/or antihypercalcemic agents for malignant cells such as VX2-L.

L27 ANSWER 32 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:833305 HCAPLUS
DOCUMENT NUMBER: 137:333131
TITLE: Methods of treating multiple myeloma and myeloma-induced **bone** resorption using **integrin** antagonists
INVENTOR(S): Mundy, Gregory R.; **Yoneda, Toshiyuki**
PATENT ASSIGNEE(S): Board of Regents, The University of Texas System, USA
SOURCE: U.S. Pat. Appl. Publ., 64 pp., Cont.-in-part of U.S. Ser. No. 943,659.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002159998	A1	20021031	US 2002-86217	20020221
WO 2000015247	A2	20000323	WO 1999-US21170	19990913
WO 2000015247	A3	20000525		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,

DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002022028	A1	20020221	US 2001-805840	20010313
US 2002041874	A1	20020411	US 2001-943659	20010831

PRIORITY APPLN. INFO.:

US 1998-100182P	P	19980914
WO 1999-US21170	A1	19990913
US 2001-805840	A2	20010313
US 2001-943659	A2	20010831

AB Antagonists of .alpha.4 **integrin**/.alpha.4 **integrin** ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing **bone** destruction assocd. with multiple myeloma. The homing of multiple myeloma cells to **bone** marrow and their .alpha.4 **integrin**-dependent release of **bone** -resorbing factors, resulting in **bone** destruction in patients with multiple myeloma, is inhibited.

L27 ANSWER 33 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:511562 HCAPLUS
DOCUMENT NUMBER: 138:22621
TITLE: Role of cell adhesion molecules in **bone** metastasis
AUTHOR(S): **Yoneda, Toshiyuki**
CORPORATE SOURCE: Department of Biochemistry, Osaka University Graduate School of Dentistry, Japan
SOURCE: Clinical Calcium (2002), 12(5), 620-625
CODEN: CLCCEJ; ISSN: 0917-5857
PUBLISHER: Iyaku Janarusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Malignant cells non-randomly and preferentially disseminated to certain distant organs. Of note, breast, prostate and lung cancer and multiple myeloma have a strong predilection for spreading to the **bone**. One of the proposed mechanisms is that these cancer cells express receptors and corresponding cell adhesion mols. (CAMs) for the extracellular matrixes (ECMs) and CAMs that are present in the **bone** microenvironment. Here, the role of **integrins** and cadherins in **bone** metastasis will be described.

L27 ANSWER 34 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:276427 HCAPLUS
DOCUMENT NUMBER: 136:304051
TITLE: Methods of treating multiple myeloma and myeloma-induced **bone** resorption using **integrin** antagonists
INVENTOR(S): Mundy, Gregory R.; **Yoneda, Toshiyuki**
PATENT ASSIGNEE(S): Board of Regents, University of Texas System, USA
SOURCE: U.S. Pat. Appl. Publ., 61 pp., Cont.-in-part of U.S. Ser. No. 805,840.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002041874	A1	20020411	US 2001-943659	20010831
WO 2000015247	A2	20000323	WO 1999-US21170	19990913
WO 2000015247	A3	20000525		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002022028	A1	20020221	US 2001-805840	20010313
US 2002159998	A1	20021031	US 2002-86217	20020221

PRIORITY APPLN. INFO.:

US 1998-100182P	P	19980914
WO 1999-US21170	W	19990913
US 2001-805840	A2	20010313
US 2001-943659	A2	20010831

AB Antagonists of .alpha.4 **integrin**/.alpha.4 **integrin** ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing **bone** destruction assocd. with multiple myeloma. The homing of multiple myeloma cells to **bone** marrow and their .alpha.4 **integrin**-dependent release of **bone** -resorbing factors, resulting in **bone** destruction in patients with multiple myeloma, is inhibited. Among the examples provided are 2 which show that monoclonal antibody PS/2 to VLA-4 strongly inhibits the growth of established myeloma cells and that anti-.alpha.4 **integrin** antibody enhances sensitivity of myeloma cells to melphalan.

L27 ANSWER 35 OF 71 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:935786 HCAPLUS
DOCUMENT NUMBER: 136:48810
TITLE: Full-length cDNA clones for polypeptide hormone phosphatonin and its use in drug screening
INVENTOR(S): Kurokawa, Tomofumi; Yamada, Takao; Morimoto, Shigeto
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001098495	A1	20011227	WO 2001-JP5263	20010620

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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AU 2001074566	A5	20020102	AU 2001-74566	20010620
JP 2002335973	A2	20021126	JP 2001-186905	20010620
EP 1293568	A1	20030319	EP 2001-941123	20010620

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: JP 2000-191088 A 20000621
WO 2001-JP5263 W 20010620

AB The present invention relates to full-length cDNA clones for a previously isolated human protein phosphatonin, having phospho-diuretic, hypophosphatemia induction, sodium-dependent phosphate transport inhibition , and/or 25-hydroxyvitamin D3-1.alpha.-hydroxylase activity regulation effect, and use in drug screening. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this human protein. The invention further relates to methods useful for diagnosis and therapy for disorders related to this novel human protein. Screening for receptor agonists or antagonists, and proteinase inhibitors, as drug candidates are claimed. Full-length cDNA clones contg. the sequence coding for a fragment previously reported (WO 9960017) were obtained from a human cDNA library derived from oncogenic hypophosphatemic **osteomalacia** (OHO). patient. The encoded protein has 525 amino acids, having extra 95 amino acids including the initial Met to the N-terminal of the fragment reported in WO 9960017. The rest of the sequence was identical except for a nucleotide at 293 position (C for G), causing an amino acid substitution (Leu for Val). Various motifs, such as **glycosaminoglycan** attachment sites, RGD sequence, myristoylation sites, phosphorylation sites for protein kinase C, casein kinase II, cAMP-dependent protein kinase, or tyrosine kinase, were identified by sequence anal. Phosphorylation by casein kinase II was demonstrated for the recombinant phosphatonin expressed in E. coli. Prodn. of antibodies and use in establishment of ELISA for phosphatonin detection is also described. Recombinant expression in CHO cells and demonstration of phosphate intake inhibition in proximal renal tubule epithelial cells, are also described.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 36 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730817 HCAPLUS
DOCUMENT NUMBER: 135:268198
TITLE: Sequences of human oncogenic **osteomalacia** -related protein 1 (OOM-1) and therapeutic uses thereof
INVENTOR(S): Schiavi, Susan; Madden, Stephen; Manavalan, Parthasarathy; Levine, M. D. Michael; Jan De Beur, Suzanne
PATENT ASSIGNEE(S): Genzyme Corporation, USA; Johns Hopkins University
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072826	A2	20011004	WO 2001-US9289	20010322
WO 2001072826	A3	20020523		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,

HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002102641 A1 20020801 US 2001-814550 20010322
PRIORITY APPLN. INFO.: US 2000-191786P P 20000324
US 2000-241598P P 20001019

AB The invention provides sequences of protein and cDNA of human oncogenic **osteomalacia**-related protein (OOM-1). The invention also provides expression systems, including gene delivery vehicles such as liposomes and vectors, and host cells contg. the polynucleotides. The present invention further provides proteins encoded by the polynucleotides, antisense oligonucleotides, antibodies that specifically recognize and bind to these proteins, as well as hybridoma cell lines. In particular, the invention discloses that the proteins are involved in modulating **bone** mineralization and phosphate metab. The invention also provides methods of monitoring expression of the gene and detecting neoplastic cells assocd. with oncogenic **osteomalacia**. The invention discloses methods for modulating **bone** mineralization activity and phosphate metab. as well as methods for treating diseases related to abnormal **bone** mineralization and abnormal phosphate metab.

L27 ANSWER 37 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:654733 HCAPLUS
DOCUMENT NUMBER: 135:206498
TITLE: Sequences of Mammalian **osteoregulins** and therapeutic uses thereof
INVENTOR(S): Brown, Thomas Aquinas; De Wet, Jeffrey Roux; Gowen, Lori Christine; Hames, Lynn Marie
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 90 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1130098	A2	20010905	EP 2001-301768	20010227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001321187	A2	20011120	JP 2001-55757	20010228

PRIORITY APPLN. INFO.: US 2000-185617P P 20000229
US 2000-234500P P 20000922

AB The invention provides a novel cDNA transcript expressed specifically in rat **osteoblasts** and **osteocytes** that encodes a 45 kDa polypeptide. The mouse and human forms of this novel protein are also identified. Characterization revealed the protein to be a secreted, RGD motif contg. protein with a limited homol. to dmpl, an extracellular matrix protein present in **bone** and teeth. Thus, this mammalian protein is designated as "**osteoregulin**.". Further studies of **osteoregulin** expression patterns and function have confirmed that **osteoregulin** plays an important role in controlling **bone** homeostasis, adipose regulation, and the calcification of atherosclerotic plaques. The invention features novel **osteoregulin**

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polypeptides, nucleic acid sequences which encode the polypeptides, vectors, antibodies, hosts which express heterologous **osteoregulins**, and animal cells and mammals with a targeted disruption of an **osteoregulin** gene. These **osteoregulins** play a role in regulating **bone** homeostasis, adiposity, and the calcification of atherosclerotic plaques. Accordingly, the invention also features screening assays to identify modulators of **osteoregulin** activity as well as methods of treating mammals for diseases or disorders assocd. with **osteoregulin** activity.

L27 ANSWER 38 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:634531 HCAPLUS
DOCUMENT NUMBER: 136:258038
TITLE: Analysis of the chromosome sequence of the legume symbiont Sinorhizobium meliloti strain 1021
AUTHOR(S): Capela, Delphine; Barloy-Hubler, Frederique; Gouzy, Jerome; Bothe, Gordana; Ampe, Frederic; Batut, Jacques; Boistard, Pierre; Becker, Anke; Boutry, Marc; Cadieu, Edouard; Dreano, Stephane; Gloux, Stephanie; Godrie, Therese; Goffeau, Andre; Kahn, Daniel; Kiss, Erno; Lelaure, Valerie; Masuy, David; Pohl, Thomas; Portetelle, Daniel; Puhler, Alfred; Purnelle, Benedicte; Ramsperger, Ulf; Renard, Clotilde; Thebault, Patricia; Vandenbol, Micheline; Weidner, Stefan; Galibert, Francis
CORPORATE SOURCE: Laboratoire de Biologie Moleculaire des Relations Plantes-Microorganismes, Unite Mixte de Recherche (UMR) 215 Centre National de la Recherche Scientifique (CNRS), Institut National de la Recherche Agronomique, Chemin, Tolosan, F-31326, Fr.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(17), 9877-9882
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sinorhizobium meliloti is an .alpha.-proteobacterium that forms agronomically important N2-fixing root nodules in legumes. We report here the complete sequence of the largest constituent of its genome, a 62.7% GC-rich 3654,135-bp circular chromosome. Annotation allowed assignment of a function to 59% of the 3341 predicted protein-coding ORFs, the rest exhibiting partial, weak, or no similarity with any known sequence. Unexpectedly, the level of reiteration within this replicon is low, with only two genes duplicated with more than 90% nucleotide sequence identity, transposon elements accounting for 2.2% of the sequence, and a few hundred short repeated palindromic motifs (RIME1, RIME2, and C) widespread over the chromosome. Three regions with a significantly lower GC content are most likely of external origin. Detailed annotation revealed that this replicon contains all housekeeping genes except two essential genes that are located on pSymB. Amino acid/peptide transport and degrdn. and sugar metab. appear as two major features of the S. meliloti chromosome. The presence in this replicon of a large no. of nucleotide cyclases with a peculiar structure, as well as of genes homologous to virulence determinants of animal and plant pathogens, opens perspectives in the study of this bacterium both as a free-living soil microorganism and as a plant symbiont.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Kam 09/812,485

L27 ANSWER 39 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:444217 HCAPLUS
DOCUMENT NUMBER: 136:162014
TITLE: MEPE, the gene encoding a tumor-secreted protein in oncogenic hypophosphatemic **osteomalacia**, is expressed in **bone**
AUTHOR(S): Argiro, L.; Desbarats, M.; Glorieux, F. H.; Ecarot, B.
CORPORATE SOURCE: Genetics Unit, Shriners Hospital, Montreal, QC, H3G 1A6, Can.
SOURCE: Genomics (2001), 74(3), 342-351
CODEN: GNMCEP; ISSN: 0888-7543
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The MEPE (matrix extracellular phosphoglycoprotein) gene is a strong candidate for the tumor-derived phosphaturic factor in oncogenic hypophosphatemic **osteomalacia** (OHO). X-linked hypophosphatemia (XLH) is phenotypically similar to OHO and results from mutations in PHEX, a putative metallopeptidase believed to process a factor(s) regulating **bone** mineralization and renal phosphate reabsorption. Here we report the isolation of the murine homolog of MEPE, from a **bone** cDNA library, that encodes a protein of 433 amino acids, 92 amino acids shorter than human MEPE. Mepe, like Phex, is expressed by fully differentiated **osteoblasts** and down-regulated by 1,25-(OH)2D3. In contrast to Phex, Mepe expression is markedly increased during **osteoblast**-mediated matrix mineralization. Greater than normal Mepe mRNA levels were obsd. in **bone** and **osteoblasts** derived from Hyp mice, the murine homolog of human XLH. Our data provide the first evidence that MEPE/Mepe is expressedby **osteoblasts** in assocn. with mineralization. (c) 2001 Academic Press.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 40 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338717 HCAPLUS
DOCUMENT NUMBER: 134:348627
TITLE: Cloning of a novel polypeptide hormone phosphatonin and its use in treating disorders of phosphate metabolism, vitamin D metabolism, skeletal mineralization, and skeletal formation
INVENTOR(S): Rowe, Peter
PATENT ASSIGNEE(S): University College London, UK
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032878	A2	20010510	WO 2000-EP10747	20001031
WO 2001032878	A3	20011115		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

Search completed by David Schreiber 308-4292

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1230369	A2	20020814	EP 2000-971403	20001031
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003513631	T2	20030415	JP 2001-535560	20001031
US 2003064498	A1	20030403	US 2002-132920	20020425

PRIORITY APPLN. INFO.:	US 1999-434185	A	19991104
	GB 1999-26424	A	19991108
	WO 2000-EP10747	W	20001031

AB The present invention relates to a novel human protein called phosphatonin, and isolated polynucleotides encoding this protein. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this human protein. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to this novel human protein. The specific conditions that can be treated include disorders of phosphate metab., vitamin D metab., skeletal mineralization, and skeletal formation.

L27 ANSWER 41 OF 71 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2000:796309 HCAPLUS
TITLE:	Design and synthesis of 5-substituted pyrrolidinone-containing antagonists of the avb3 receptor.
AUTHOR(S):	Perkins, James J.; Meissner, Robert S.; Duggan, Mark E.; Hartman, George D.; Duong, Le T.; Lynch, Joseph J., Jr.; Fernandez-Metzler, Carmen; Bennett, Ma; Merkle, Kara; Libby, Laura; Leu, Chih-Tai; Nagy, Rose; Prueksaritanont, Thomayant; Rodan, Gideon; Rodan, Sevgi; Stump, Gary; Wallace, Audrey; Wesolowski, Gregg A.
CORPORATE SOURCE:	Medicinal Chemistry, Merck and Co. Inc, West Point, PA, 19486, USA
SOURCE:	Abstracts of Papers - American Chemical Society (2000), 220th, MEDI-310 CODEN: ACSRAL; ISSN: 0065-7727
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal; Meeting Abstract
LANGUAGE:	English

AB The vitronectin receptor avb3 is a member of the integrin family of receptors and is highly expressed in osteoclasts, cells which are responsible for the **resorption** of **bone**. Antibodies to avb3 and the **peptide** echistatin have been shown to inhibit **bone resorption** in vitro and in vivo. More recently, small-mol. mimetics of the RGD amino acid triad have been reported to inhibit **bone resorption** in vivo. The trends in **integrin binding** affinity and pharmacokinetic profile for several 5-substituted pyrrolidinone-contg. avb3 antagonists will be presented. An efficient and stereoselective synthetic route to this class of antagonists will be described. The installation of structural diversity about the pyrrolidinone core relies on cuprate-mediated alkylations of an a intermediate iodide or tosylate.

L27 ANSWER 42 OF 71 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2000:578625 HCAPLUS
DOCUMENT NUMBER:	134:1213
TITLE:	MEPE, a new gene expressed in **bone** marrow and tumors causing **osteomalacia**

Kam 09/812,485

AUTHOR(S): Rowe, Peter S. N.; De Zoysa, Priyal A.; Dong, Rong; Wang, Huei Rong; White, Kenneth E.; Econs, Michael J.; Oudet, Claudine L.
CORPORATE SOURCE: Centre for Molecular Osteo-Renal Research, Department of Biochemistry and Molecular Biology, Royal Free and University College Medical School, London, NW3 2PF, UK
SOURCE: Genomics (2000), 67(1), 54-68
CODEN: GNMCEP; ISSN: 0888-7543
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oncogenic hypophosphatemic **osteomalacia** (OHO) is characterized by a renal phosphate leak, hypophosphatemia, low-serum calcitriol (1,25-vitamin-D3), and abnormalities in skeletal mineralization. Resection of OHO tumors results in remission of the symptoms, and there is evidence that a circulating phosphaturic factor plays a role in the **bone** disease. This paper describes the characterization and cloning of a gene that is a candidate for the tumor-secreted phosphaturic factor. This new gene has been named MEPE (matrix extracellular phosphoglycoprotein) and has major similarities to a group of **bone** -tooth mineral matrix phosphoglycoproteins (**osteopontin** (OPN; HGMW-approved symbol SPP1), dentin sialo phosphoprotein (DSPP), dentin matrix protein 1 (DMP1), **bone** sialoprotein II (IBSP), and **bone** morphogenetic proteins (BMP)). All the proteins including MEPE contain RGD sequence motifs that are proposed to be essential for **integrin**-receptor interactions. Of further interest is the finding that MEPE, OPN, DSPP, DMP1, IBSP, and BMP3 all map to a defined region in chromosome 4q. Refined mapping localizes MEPE to 4q21.1 between ESTs D4S2785 (WI-6336) and D4S2844 (WI-3770). MEPE is 525 residues in length with a short N-terminal signal peptide. High-level expression of MEPE mRNA occurred in all four OHO tumors screened. Three of 11 non-OHO tumors screened contained trace levels of MEPE expression (detected only after RT-PCR and Southern 32P anal.). Normal tissue expression was found in **bone** marrow and brain with very-low-level expression found in lung, kidney, and human placenta. Evidence is also presented for the tumor secretion of clusterin (HGMW-approved symbol CLU) and its possible role as a cytotoxic factor in one of the OHO patients described. (c) 2000 Academic Press.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 43 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:190945 HCAPLUS
DOCUMENT NUMBER: 132:250007
TITLE: Methods of treating multiple myeloma and myeloma-induced **bone** resorption using **integrin** antagonists
INVENTOR(S): Mundy, Gregory R.; **Yoneda, Toshiyuki**
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015247	A2	20000323	WO 1999-US21170	19990913

Search completed by David Schreiber 308-4292

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     WO 2000015247      A3    20000525
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2343579         AA    20000323        CA 1999-2343579   19990913
     AU 9962486         A1    20000403        AU 1999-62486     19990913
     BR 9913705         A     20010605        BR 1999-13705     19990913
     EP 1113810         A2    20010711        EP 1999-949656    19990913
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     EE 200100146       A     20020617        EE 2001-20010014619990913
     JP 2002524529      T2    20020806        JP 2000-569831    19990913
     NO 2001001244      A     20010514        NO 2001-1244      20010312
     US 2002022028      A1    20020221        US 2001-805840    20010313
     US 2002041874      A1    20020411        US 2001-943659    20010831
     US 2002159998      A1    20021031        US 2002-86217     20020221
PRIORITY APPLN. INFO.:                     US 1998-100182P  P  19980914
                                           WO 1999-US21170  W  19990913
                                           US 2001-805840   A2 20010313
                                           US 2001-943659   A2 20010831
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AB Antagonists of .alpha.4 **integrin**/.alpha.4 **integrin** ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing **bone** destruction assocd. with multiple myeloma. The homing of multiple myeloma cells to **bone** marrow and their .alpha.4 **integrin**-dependent release of **bone** -resorbing factors, resulting in **bone** destruction in patients with multiple myeloma, is inhibited. The .alpha.4 **integrin** or ligand antagonist is an antibody, humanized antibody, chimeric antibody, human antibody or fragment, such as anti-VLA-4 or anti-VCAM-1 antibody.


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ACCESSION NUMBER:         1999:795994  HCAPLUS
DOCUMENT NUMBER:          132:31744
TITLE:                    Gene probes used for genetic profiling in healthcare
                          screening and planning
INVENTOR(S):              Roberts, Gareth Wyn
PATENT ASSIGNEE(S):       Genostic Pharma Ltd., UK
SOURCE:                   PCT Int. Appl., 745 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
     ---------------    ----  --------      ---------------   --------
     WO 9964627         A2    19991216      WO 1999-GB1780    19990604
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
             DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
             JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
             MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
             TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
             MD, RU, TJ, TM
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L27 ANSWER 45 OF 71 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1999:753255 HCAPLUS
DOCUMENT NUMBER:	132:722
TITLE:	Cloning of human polypeptide hormone phosphatonin involved in phosphate metabolism
INVENTOR(S):	Rowe, Peter
PATENT ASSIGNEE(S):	University College London, UK
SOURCE:	PCT Int. Appl., 136 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English

Search completed by David Schreiber 308-4292

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9960017	A2	19991125	WO 1999-EP3403	19990518
WO 9960017	A3	20000309		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2329054	AA	19991125	CA 1999-2329054	19990518
AU 9943624	A1	19991206	AU 1999-43624	19990518
GB 2339572	A1	20000202	GB 1999-11577	19990518
EP 1086225	A2	20010328	EP 1999-926320	19990518
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE, FI				
JP 2002515232	T2	20020528	JP 2000-549635	19990518

PRIORITY APPLN. INFO.:
GB 1998-10681 A 19980518
GB 1998-19387 A 19980904
WO 1999-EP3403 W 19990518

AB The present invention relates to a novel human protein called phosphatonin (also known as Metastatic-tumor Excreted Phosphaturic-Element or MEPE), and isolated polynucleotides encoding this protein. Phosphatonin modulates Na+-dependent phosphate co-transport, vitamin D metab. via renal 25-hydroxyvitamin D3 24-hydroxylase or 25-hydroxyvitamin D3 1.alpha.-hydroxylase, and/or **bone** mineralization. Phosphatonin was isolated from a cDNA library constructed form mRNA extd. from a meningeal phosphaturic-mesenchymal-tumor resected from a patient suffering from oncogenic hypophosphatemic **osteomalacia**. The cDNA codes for a protein 430 amino acids in length. Phosphatonin may be cleaved proteolytically in vivo, for example by the PHEX metalloendopeptidase. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this human protein. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to this novel human protein.

L27 ANSWER 46 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:3293 HCAPLUS
DOCUMENT NUMBER: 130:61099
TITLE: **Peptides** for altering **bone** **resorption**, angiogenesis and restenosis
INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg F.
PATENT ASSIGNEE(S): La Jolla Cancer Research Foundation, USA
SOURCE: U.S., 90 pp., Cont.-in-part of U.S. Ser. No. 303,052.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5849865	A	19981215	US 1995-421695	19950412

US 5770565	A	19980623	US 1994-303052	19940908
PRIORITY APPLN. INFO.:			US 1994-227316	19940413
			US 1994-303052	19940908

AB The invention provides Arg-Gly-Asp **peptides** that can alter the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. The invention also provides methods of using the Arg-Gly-Asp **peptides** to alter .alpha.v.beta.3 **integrin** receptor-mediated **binding** of a cell such as an osteoclast, endothelial cell or smooth muscle cell to a matrix. The invention further provides methods for ameliorating the severity of a pathol. characterized, in part, by an undesirable level of **bone resorption**, angiogenesis or restenosis in a subject.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 47 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:623982 HCAPLUS
DOCUMENT NUMBER: 129:239918
TITLE: RGD **peptides** useful for altering **bone resorption**
INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg F.
PATENT ASSIGNEE(S): La Jolla Cancer Research Center, USA
SOURCE: U.S., 87 pp., Cont.-in-part of U.S. Ser. No. 303,052. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5807819	A	19980915	US 1995-421698	19950412
US 5770565	A	19980623	US 1994-303052	19940908
PRIORITY APPLN. INFO.:			US 1994-227316	19940415
			US 1994-303052	19940908

OTHER SOURCE(S): MARPAT 129:239918

AB Arg-Gly-Asp (RGD) **peptides** are provided that can alter the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. Also provided are methods of using the RGD **peptides** to alter .alpha.V.beta.3 **integrin** receptor-mediated **binding** of a cell such as an osteoclast, endothelial cell or smooth muscle cell to a matrix. The invention further provides methods for ameliorating the severity of a pathol. characterized, in part, by an undesirable level of **bone resorption**, angiogenesis or restenosis in a subject.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 48 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:581524 HCAPLUS
DOCUMENT NUMBER: 129:313728
TITLE: Integrin-mediated signaling in the regulation of osteoclast adhesion and activation
AUTHOR(S): Duong, Le T.; Rodan, Gideon A.
CORPORATE SOURCE: Dep. of Bone Biol. and Osteoporosis, Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Frontiers in Bioscience [Electronic Publication]

(1998), 3, D757-D768
CODEN: FRBIF6
URL: http://www.bioscience.org/1998/v3/d/duong/d757-768.htm
PUBLISHER: Frontiers in Bioscience
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review with 125 refs. Integrins are heterodimeric membrane receptors that mediate cell-extracellular matrix (ECM), and cell-cell interactions. Integrins provide a phys. link between the ECM and the cell cytoskeleton, and transduce signals which lead to elevation of cytosolic pH and calcium levels, changes in phospholipid metab. and ultimately regulate gene expression. Osteoclast **bone resorption** is a complicated multistep process, that starts with matrix recognition, osteoclast attachment, polarization and formation of the sealing zone on the bone, followed by the directional secretion of acids and lysosomal enzymes to the resorbing surface. Osteoclasts exhibit high expression of the .alpha.v.beta.3 **integrin**, which **binds** to a variety of RGD-contg. proteins including vitronectin, osteopontin and bone sialoprotein. RGD-contg. **peptides**, RGD-mimetics and blocking antibodies to .alpha.v.beta.3 integrins were shown to inhibit **bone resorption** in vitro and in vivo, suggesting that this integrin plays an important role in regulating osteoclast activity. Furthermore, RGD-contg. **peptides** and proteins modulate osteoclastic cytosolic calcium levels. Phosphatidyl inositol 3-kinase and c-Src were co-immunopptd. with alpha .alpha.v.beta.3 integrins in these cells. In addn., c-Cbl was found to be a substrate of c-Src in osteoclasts. More recently, ligand-engagement or clustering of .alpha.v.beta.3 integrins in osteoclasts induced tyrosine phosphorylation of PYK2, a member of the focal adhesion kinase family, and of p130cas, a substrate of v-Src and v-Crk. Both PYK2 and p130cas were also found in the sealing zone of actively resorbing osteoclasts. How these signaling mols. interact with each other in mediating the .alpha.v.beta.3 rate limiting effect on **bone resorption** is not well understood. They emerged however as key players in linking the adhesion of osteoclasts to the bone matrix, to cytoskeletal organization, and to the polarization and activation of these cells for **bone resorption**.

L27 ANSWER 49 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:545397 HCAPLUS
DOCUMENT NUMBER: 129:170543
TITLE: Use of RGD **peptides** for altering **bone resorption** and **integrin binding**
INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg F.
PATENT ASSIGNEE(S): La Jolla Cancer Research Center, USA
SOURCE: U.S., 88 pp., Cont.-in-part of U. S. 303,052.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5792745	A	19980811	US 1995-421697	19950412
US 5770565	A	19980623	US 1994-303052	19940908
PRIORITY APPLN. INFO.:			US 1994-227316	19940413

Search completed by David Schreiber 308-4292

US 1994-303052 19940908
OTHER SOURCE(S): MARPAT 129:170543
AB The invention provides Arg-Gly-Asp **peptides** that can alter the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. The invention also provides methods of using the Arg-Gly-Asp **peptides** to alter .alpha.v.beta.3 **integrin** receptor-mediated **binding** of a cell such as an osteoclast, endothelial cell, or smooth muscle cell to a matrix. The invention further provides methods for ameliorating the severity of a pathol. characterized, in part, by an undesirable level of **bone resorption**, angiogenesis or restenosis in a subject.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 50 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:441958 HCAPLUS
DOCUMENT NUMBER: 129:104233
TITLE: Use of cyclic RGD **peptides** for altering .alpha.v.beta.3 -mediated binding
INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg F.
PATENT ASSIGNEE(S): La Jolla Cancer Research Center, USA
SOURCE: U.S., 87 pp., Cont.-in-part of U. S. Ser. No. 303,052. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5773412	A	19980630	US 1995-421696	19950412
US 5770565	A	19980623	US 1994-303052	19940908

PRIORITY APPLN. INFO.: US 1994-227316 19940413
US 1994-303052 19940908
OTHER SOURCE(S): MARPAT 129:104233
AB The present invention provides cyclic Arg-Gly-Asp **peptides** that can alter the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. The invention also provides methods of using the Arg-Gly-Asp **peptides** to alter .alpha.v.beta.3 **integrin** receptor-mediated **binding** of a cell such as an osteoclast, endothelial cell or smooth muscle cell to a matrix. The invention further provides methods for ameliorating the severity of a pathol. characterized, in part, by an undesirable level of **bone resorption**, angiogenesis or restenosis in a subject. **Peptide** RGD(YOMe)RE-NH2 was particularly effective in inhibiting platelet aggregation at low concns. and was relatively potent for binding .alpha.v.beta.3. This **peptide** can, therefore, be useful for reducing or preventing restenosis.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 51 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:435742 HCAPLUS
DOCUMENT NUMBER: 129:90465
TITLE: **Peptides** for reducing or inhibiting **bone resorption**

Kam 09/812,485

INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg
PATENT ASSIGNEE(S): La Jolla Cancer Research Center, USA
SOURCE: U.S., 71 pp., Cont.-in-part of U. S. Ser. No. 227,316, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5770565	A	19980623	US 1994-303052	19940908
WO 9528426	A2	19951026	WO 1995-US4741	19950412
WO 9528426	A3	19951214		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2187642	AA	19951026	CA 1995-2187642	19950412
AU 9523573	A1	19951110	AU 1995-23573	19950412
AU 691918	B2	19980528		
EP 755408	A1	19970129	EP 1995-917573	19950412
R: BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
JP 10502053	T2	19980224	JP 1995-527159	19950412
US 5759996	A	19980602	US 1995-421702	19950412
US 5773412	A	19980630	US 1995-421696	19950412
US 5792745	A	19980811	US 1995-421697	19950412
US 5807819	A	19980915	US 1995-421698	19950412
US 5849865	A	19981215	US 1995-421695	19950412
EP 896003	A1	19990210	EP 1998-250297	19950412
R: BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				

PRIORITY APPLN. INFO.:	US 1994-227316	19940413
	US 1994-303052	19940908
	EP 1995-917573	19950412
	WO 1995-US4741	19950412

OTHER SOURCE(S): MARPAT 129:90465

AB The present invention provides Arg-Gly-Asp **peptides** that can reduce or inhibit the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. The invention also provides methods of using the Arg-Gly-Asp **peptides** to reduce or inhibit osteoclast binding to a matrix, to reduce or inhibit **bone resorption** in a subject and to alter .alpha.V .beta.3 binding.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 52 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:392140 HCAPLUS
DOCUMENT NUMBER: 129:49657
TITLE: RGD **peptides** useful for altering .alpha.v.beta.3 -mediated binding in treatment of angiogenesis or **bone-resorption** disorders
INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg F.

Search completed by David Schreiber 308-4292

Kam 09/812,485

PATENT ASSIGNEE(S): La Jolla Cancer Research Center, USA
SOURCE: U.S., 90 pp., Cont.-in-part of U. S. Ser. No. 303,052.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5759996	A	19980602	US 1995-421702	19950412
US 5770565	A	19980623	US 1994-303052	19940908

PRIORITY APPLN. INFO.: US 1994-227316 19940413
US 1994-303052 19940908
OTHER SOURCE(S): MARPAT 129:49657
AB The present invention provides Arg-Gly-Asp **peptides** that can alter the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. The invention also provides methods of using the Arg-Gly-Asp **peptides** to alter .alpha.v.beta.3 **integrin** receptor-mediated **binding** of a cell such as an osteoclast, endothelial cell or smooth muscle cell to a matrix. The invention further provides methods for ameliorating the severity of a pathol. characterized, in part, by an undesirable level of **bone resorption**, angiogenesis or restenosis in a subject.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 53 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:107400 HCAPLUS
DOCUMENT NUMBER: 126:122510
TITLE: Modified **osteogenic** materials comprising collagen and demineralized bone particles
INVENTOR(S): Jefferies, Steven R.
PATENT ASSIGNEE(S): Biocoll Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9639203	A1	19961212	WO 1996-US9749	19960606
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2222626	AA	19961212	CA 1996-2222626	19960606
AU 9661074	A1	19961224	AU 1996-61074	19960606
EP 851772	A1	19980708	EP 1996-918400	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192700	A	19980909	CN 1996-196049	19960606

PRIORITY APPLN. INFO.: US 1995-469982 19950606
WO 1996-US9749 19960606

Search completed by David Schreiber 308-4292

AB An **osteogenic** process and product comprise collagen and demineralized bone particles. The product may contain a max. of 20% by wt. inorg. materials. The product may be densified by compression. Addnl. **osteogenic** factors, mitogens, drugs or antibiotics may be incorporated therein. Inorg. materials may be bound to the org. matrix via precoating with a **calcium** or hydroxyapatite **binding** protein, **peptide** or amino acid. The materials also display long lasting drug release characteristics. The process and resultant compn. increases the rate and predictability of osteoinduction by demineralized bone matrix. In particular, this invention relates to compns. of demineralized bone and calcium or other mineral salts which exhibit enhanced **osteogenic** potential. The **osteogenic** compns. comprise between about 60% to 90% demineralized bone and compns. comprising a carrier and alk. phosphatase capable of inducing bone-like structures. Thus, 10 g of demineralized bone matrix was milled to a uniform particle size ranging 75-400.mu.m. The particles were immersed in a soln. of 0.05% glutaraldehyde in neutral phosphate buffered isotonic saline for 12 h with const. agitation at 4.degree., then filtered, washed, dried and sterilized. These activated particles may be placed directly in an osseous defect or complexed with an org. biopolymer and used.

L27 ANSWER 54 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:425025 HCAPLUS
DOCUMENT NUMBER: 125:111473
TITLE: Cytoplasmic signaling in metastatic breast cancer cells colonized in **bone** microenvironment
AUTHOR(S): **Yoneda, Toshiyuki**
CORPORATE SOURCE: Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284, USA
SOURCE: Jikken Igaku (1996), 14(10), 1454-1458
CODEN: JIIGEF; ISSN: 0288-5514
PUBLISHER: Yodosha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 26 refs., on **integrin, osteopontin,** insulin-like growth factor, tyrosine kinase, etc., in relation to activation of intracellular signaling of tumor tissue by contacting with **bone** cell and interaction between **osteoclast** and metastatic tumor cell.

L27 ANSWER 55 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:335060 HCAPLUS
DOCUMENT NUMBER: 125:105315
TITLE: Fetuin/.alpha.2-HS glycoprotein is a transforming growth factor-.beta. type II receptor mimic and cytokine antagonist
AUTHOR(S): Demetriou, Michael; Binkert, Christoph; Sukhu, Balram; Tenenbaum, Howard C.; Dennis, James W.
CORPORATE SOURCE: Samuel Lunenfeld Res. Inst., Mt. Sinai Hosp., Toronto, ON, M5G 1X5, Can.
SOURCE: Journal of Biological Chemistry (1996), 271(22), 12755-12761
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The serum glycoprotein fetuin is expressed during embryogenesis in multiple tissues including limb buds and has been shown to promote bone

remodeling and stimulate cell proliferation in vitro. In this report, we demonstrate that fetuin antagonizes the antiproliferative action of transforming growth factor-.beta.1 (TGF-.beta.1) in cell cultures. Surface plasmon resonance measurements show that fetuin binds directly to TGF-.beta.1 and TGF-.beta.2 and with greater affinity to the TGF-.beta.-related bone morphogenetic proteins (BMP-2, BMP-4, and BMP-6). In a competitive ELISA, fetuin blocked binding of TGF-.beta.1 to the extracellular domain of TGF-.beta. receptor type II (T.beta.RII), one of the primary TGF-.beta.-binding receptors. A comparison of fetuin and T.beta.RII shows homol. in an 18-19-amino acid sequence, which we have designated TGF-.beta. receptor II homol. 1 domain (TRH1). Since the TRH1 sequence is known to form a disulfide loop in fetuin, cyclized TRH1 **peptides** from both fetuin and T.beta.RII were chem. synthesized and tested for cytokine binding activity. Cyclized TRH1 **peptide** from T.beta.RII bound to TGF-.beta.1 with greater affinity than to BMP-2, while the cyclized TRH1 **peptide** from fetuin bound preferentially to BMP-2. Finally, fetuin or neutralizing anti-TGF-.beta. antibodies blocked **osteogenesis** and deposition of calcium-contg. matrix in cultures of dexamethasone-treated rat bone marrow cells. In summary, these expts. define the TRH1 **peptide** loop as a cytokine-binding domain in both T.beta.RII and fetuin and suggest that fetuin is a natural antagonist of TGF-.beta. and BMP activities.

L27 ANSWER 56 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:997347 HCAPLUS
DOCUMENT NUMBER: 124:106695
TITLE: **Peptides** for reducing or inhibiting **bone resorption**, angiogenesis and restenosis
INVENTOR(S): Cheng, Soan; Ingram, Ronald; Mullen, Daniel; Tschopp, Juerg
PATENT ASSIGNEE(S): La Jolla Cancer Research Foundation, USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9528426	A2	19951026	WO 1995-US4741	19950412
WO 9528426	A3	19951214		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5770565	A	19980623	US 1994-303052	19940908
AU 9523573	A1	19951110	AU 1995-23573	19950412
AU 691918	B2	19980528		
EP 755408	A1	19970129	EP 1995-917573	19950412
R: BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
JP 10502053	T2	19980224	JP 1995-527159	19950412

PRIORITY APPLN. INFO.: US 1994-227316 19940413
US 1994-303052 19940908
WO 1995-US4741 19950412
OTHER SOURCE(S): MARPAT 124:106695

Search completed by David Schreiber 308-4292

Kam 09/812,485

AB The present invention provides Arg-Gly-Asp (RGD) **peptides** that can alter the binding of osteoclasts to a matrix such as bone or can selectively alter **integrin** receptor **binding**. The invention also provides methods of using the Arg-Gly-Asp **peptides** to alter .alpha.v.beta.3 **integrin** receptor-mediated **binding** of a cell (e.g. an osteoclast, endothelial cell or smooth muscle cell) to a matrix. The invention further provides methods for ameliorating the severity of pathol. characterized, in part, by an undesirable level of **bone resorption**, angiogenesis, or restenosis in a subject.

L27 ANSWER 57 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:818744 HCAPLUS
DOCUMENT NUMBER: 123:220289
TITLE: Thioredoxin fusion proteins for use in the manufacture of foreign proteins in soluble forms and in their affinity purification
INVENTOR(S): Mccoy, John; Diblasio-Smith, Elizabeth; Grant, Kathleen; Lavallie, Edward R.
PATENT ASSIGNEE(S): Genetics Institute, Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516044	A2	19950615	WO 1994-US14179	19941208
WO 9516044	A3	19951019		
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5646016	A	19970708	US 1993-165301	19931210
AU 9513994	A1	19950627	AU 1995-13994	19941208

PRIORITY APPLN. INFO.:
US 1993-165301 A 19931210
US 1991-652531 B2 19910206
US 1991-745382 A2 19910814
US 1992-921848 A2 19920728
WO 1994-US14179 W 19941208

AB Fusion proteins of a thioredoxin (or thioredoxin analog) with a second protein are manufd. by expression of the corresponding gene in a bacterial host. The use of thioredoxin helps maintain the soly. of the protein and simplifies purifn. The protein may be fused to the N- or C-terminus or be placed in the middle of the thioredoxin. The fusion protein may be modified to introduce one or more metal-binding/chelating amino-acid residues to aid in purifn. The fusion protein, located in the bacterial cytoplasm, may be selectively released from the cell by osmotic shock or freeze/thaw procedures. It may be optionally cleaved to liberate the sol., correctly folded heterologous protein from the thioredoxin-like portion. The use of thioredoxin to manuf. a no. of mammalian proteins in Escherichia coli is demonstrated.

L27 ANSWER 58 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:405708 HCAPLUS
DOCUMENT NUMBER: 121:5708
TITLE: Bone matrix RGD glycoproteins: Immunolocalization and interaction with human primary osteoblastic bone cells in vitro

Search completed by David Schreiber 308-4292

AUTHOR(S): Grzesik, Wojciech J.; Robey, Pamela Gehron
CORPORATE SOURCE: Natl. Inst. Dent. Res., Natl. Inst. Health, Bethesda, MD, USA
SOURCE: Journal of Bone and Mineral Research (1994), 9(4), 487-96
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The interaction of cells with extracellular matrix is essential for their anchorage, proliferation, migration, and differentiation. In bone matrix there are multiple glycoproteins that contain the **integrin-binding** RGD sequence: fibronectin (FN), thrombospondin (TSP), osteopontin (OPN), bone sialoprotein (BSP), type I collagen (COLL I), and vitronectin (VN). In this study, the localization of TSP, FN, VN, and several integrins within developing human long bone using immunohistochem. methods was examd., as was the effect of all bone RGD proteins on the adhesion of human osteoblastic cells. Thrombospondin, fibronectin, and vitronectin showed distinct localization patterns within bone tissue. TSP was found mainly in osteoid and the periosteum; VN appeared to be present mainly in mature bone matrix. FN was present in the periosteum as well as within both mature and immature bone matrix. Using a panel of antiintegrin antibodies the authors found that bone cells in vivo and in vitro express .alpha.4, .alpha.v, .alpha.5.beta.1, .alpha.v.beta.3, and .beta.3/.beta.5 integrins, and these receptors are for the most part expressed on all bone cells at different stages of maturation with quant. rather than qual. variations, with the exception of .alpha.4, which is expressed mainly by osteoblasts. Cell attachment assays were performed using primary human cells of the osteoblastic lineage under serum-free conditions. COLL I, TSP, VN, FN, OPN, and BSP promoted bone cell attachment in a dose-dependent manner and were equiv. in action when used in equimolar concns. In the presence of GRGDS **peptide** in the medium, the adhesion to BSP, OPN, and VN was almost completely blocked (10, 10, and 15% of control, resp.), and attachment to FN, COLL I, and TSP was only slightly decreased (80, 75, and 55%, resp.). These results suggest that human bone cells may use RGD-independent mechanisms for attachment to the latter glycoproteins.

L27 ANSWER 59 OF 71 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:604376 HCAPLUS
DOCUMENT NUMBER: 115:204376
TITLE: Recognition of osteopontin and related **peptides** by an .alpha.v.beta.3 integrin stimulates immediate cell signals in osteoclasts
AUTHOR(S): Miyauchi, Akimitsu; Alvarez, Jose; Greenfield, Edward M.; Teti, Anna; Grano, Maria; Colucci, Silvia; Zambonin-Zallone, Alberta; Ross, F. Patrick; Teitelbaum, Steven L.; et al.
CORPORATE SOURCE: Jewish Hosp., Washington Univ., St. Louis, MO, 63110, USA
SOURCE: Journal of Biological Chemistry (1991), 266(30), 20369-74
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of immediate cell signals produced by occupancy of the chicken osteoclast .alpha.v.beta.3 integrin was investigated. Synthetic osteopontin and **peptides** from the osteopontin and bone sialoprotein sequences contg. Arg-Gly-Asp stimulated immediate redns. in osteoclast cytosolic Ca2+. The changes in cytosolic Ca2+ required the

Arg-Gly-Asp sequence and were blocked by a monoclonal antibody to the .alpha.v.beta.3 integrin, LM609. Osteoclast stimulation by the proteins through the integrin did not require immobilization since sol. **peptides** produced changes in cytosolic Ca2+ and inhibited osteoclast binding to **bone** particles and **bone resorption**. The decrease in cytosolic Ca2+ stimulated by osteopontin and related **peptides** appeared to be due to activation of a plasma membrane Ca2+-ATPase by calmodulin. Thus, the data suggest that ligand binding to the osteoclast .alpha.v.beta.3 integrin results in calmodulin-dependent redn. in cytosolic Ca2+ which participates in regulation of osteoclast function.

L27 ANSWER 60 OF 71 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:441568 BIOSIS
DOCUMENT NUMBER: PREV199900441568
TITLE: Anti-alpha4 **integrin** antibody suppresses the **bone** disease of myeloma and disrupts myeloma-marrow stromal cell interactions.
AUTHOR(S): Mori, Y. (1); Michigami, T. (1); Dallas, M. (1); Niewolna, M. (1); Story, B. (1); Lobb, R.; Mundy, G. R. (1); **Yoneda, T. (1)**
CORPORATE SOURCE: (1) Univ. TX Hlth. Sci. Ctr., San Antonio, TX USA
SOURCE: Journal of Bone and Mineral Research, (Sept., 1999) Vol. 14, No. SUPPL. 1, pp. S173.
Meeting Info.: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999 American Society for Bone and Mineral Research
. ISSN: 0884-0431.
DOCUMENT TYPE: Conference
LANGUAGE: English

L27 ANSWER 61 OF 71 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:224624 BIOSIS
DOCUMENT NUMBER: PREV199800224624
TITLE: Dentin matrix proteins.
AUTHOR(S): Butler, William T. (1)
CORPORATE SOURCE: (1) Dep. Basic Sci., Univ. Texas-Houston Dental Branch, 6516 John Freeman Ave., Houston, TX 77030 USA
SOURCE: European Journal of Oral Sciences, (Jan., 1998) Vol. 106, No. 1 SUPPL., pp. 204-210.
ISSN: 0909-8836.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Dentinogenesis consists of highly controlled events occurring a short distance from the periphery of odontoblasts; it involves formation of extracellular collagen fibrils that act as an undergirding for deposition of plate-like carbonate apatite crystals. Odontoblasts also form a set of matrix proteins that are probably secreted at the mineralization front. Although most of these proteins are similar to those of bone, and differ from soft tissue proteins, dentin contains two unique proteins. Dentin phosphoprotein (DPP) is rich in aspartic acid (D) and phosphoserine (S*) and **binds** large amounts of **calcium**. DPP contains repeating sequences of DS*S* and S*D in discrete areas of the protein. DS*S* repeats form ridges of phosphates and carboxyllates while the S*D sequences give rise to ridges with phosphates and carboxyllates on opposing sides of the **peptide** chain. These structures undoubtedly have functional significance since DPP is involved in promotion of mineral initiation and in control of mineral size and shape.

Search completed by David Schreiber 308-4292

Dentin sialoprotein (DSP), found only in dentin, is a 53 kDa glycoprotein rich in aspartic acid, serine, glutamic acid and glycine. DSP is made by odontoblasts and also by pre-ameloblasts, but not by osteoblasts or other cell types. The gene for DSP is now known to be continuous with that of DPP. Thus, DSP and DPP must be secreted as a single protein which is then proteolytically processed to form the individual components found in the dentin matrix. Significantly, the DSP/DPP gene has been localized to human chromosome 4q21 at a site implicated in dentinogenesis imperfecta type II.

L27 ANSWER 62 OF 71 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94318206 EMBASE
DOCUMENT NUMBER: 1994318206
TITLE: **Osteolytic bone** metastasis in breast cancer.
AUTHOR: **Yoneda T.**; Sasaki A.; Mundy G.R.
CORPORATE SOURCE: Division of Endocrinology/Metabolism, Department of Medicine, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive,San Antonio, TX 78284-7877, United States
SOURCE: Breast Cancer Research and Treatment, (1994) 32/1 (73-84). ISSN: 0167-6806 CODEN: BCTRD6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Metastasis of breast cancer cells to **bone** consists of multiple sequential steps. To accomplish the process of metastasis to **bone** , breast cancer cells are required to intrinsically possess or acquire the capacities that are necessary for them to proliferate, invade, migrate, survive, and ultimately arrest in **bone**. These capacities are essential for any cancer cells to develop distant metastases in organs such as lungs and liver as well as **bone**. Once breast cancer cells arrest in **bone**, **bone** is a storehouse of a variety of cytokines and growth factors and thus provides an extremely fertile environment for the cells to grow. However, breast cancer cells are unable to progress in **bone** unless they destroy **bone** with the assistance of **bone**- resorbing **osteoclasts**. Thus, the capacity of breast cancer cells to collaborate with **osteoclasts** is likely to be specific and is likely critical for them to cause **osteolytic bone** metastases. Evidence to support the concept that there is an intimate relationship between breast cancer cells and **osteoclasts** is described using an in vivo **bone** metastasis model in which human breast cancer cells are inoculated into the left ventricle of nude mice. The roles of cell adhesion molecules including cadherins and laminin and matrix metalloproteinases in the development of **osteolytic bone** metastases by breast cancer are also discussed.

L27 ANSWER 63 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1999:869695 SCISEARCH
THE GENUINE ARTICLE: 232CA
TITLE: Anti-alpha 4 **integrin** antibody suppresses the **bone** disease of myeloma and disrupts myeloma-marrow stromal cell interactions.
AUTHOR: Mori Y (Reprint); Michigami T; Dallas M; Niewolna M; Story B; Lobb R; Mundy G R; **Yoneda T**
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, SAN ANTONIO, TX; BIOGEN, CAMBRIDGE, MA

Search completed by David Schreiber 308-4292

COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (SEP 1999) Vol. 14, Supp. [1], pp. 1161-1161.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.
ISSN: 0884-0431.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L27 ANSWER 64 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:851199 SCISEARCH
THE GENUINE ARTICLE: 135AX
TITLE: Processing of NH2- and COOH-terminal **peptides** of rat osteocalcin by cathepsin B and cathepsin L
AUTHOR: Kobayashi Y; Sakai H (Reprint); Ikeda S; Kobayashi K; Kato Y; Mataki S
CORPORATE SOURCE: NAGASAKI UNIV, SCH DENT, DEPT PHARMACOL, DEPT ORTHODONT, 1-7-1 SAKAMOTO, NAGASAKI 8528588, JAPAN (Reprint); NAGASAKI UNIV, SCH DENT, DEPT PHARMACOL, DEPT ORTHODONT, NAGASAKI 8528588, JAPAN; TOKYO MED & DENT UNIV, FAC DENT, DEPT ORAL DIAG & GEN DENT, BUNKYO KU, TOKYO 1130034, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF BONE AND MINERAL METABOLISM, (OCT 1998) Vol. 16, No. 2, pp. 72-80.
Publisher: SPRINGER-VERLAG TOKYO, 3-3-13, HONGO, BUNKYO-KU, TOKYO 113, JAPAN.
ISSN: 0914-8779.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Rat osteocalcin was subjected to proteolysis by cathepsins B and L at acid pH in vitro. Short fragments of fewer than 8 amino acids were liberated from both the NH2 and COOH-termini of the molecule, but the midportion, composed of antiparallel alpha-helical domains, was resistant to proteolysis. Intact rat osteocalcin bound 10 Ca2+/mol protein at pH 7.5 and the binding decreased to half that amount at pH 5.0, while the midportion fragment (Ala(8)-Lys(43)) bound 4-5 Ca2+/mol protein at both pH 5.0 and 7.5. When COOH-terminal-truncated rat osteocalcin (Tyr(1)-Lys(43)) was prepared with lysyl-endopeptidase, it showed nearly the same Ca2+ binding as that of the intact molecule. Our results suggest that proteolytic processing of the terminal sequence of osteocalcin alters its intrinsic Ca2+-binding capacity and that its NH2-terminal sequence is probably involved.

L27 ANSWER 65 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:491399 SCISEARCH
THE GENUINE ARTICLE: ZV428
TITLE: Cadherin-6 mediates the heterotypic interactions between the hemopoietic **osteoclast** cell lineage and stromal cells in a murine model of **osteoclast** differentiation
AUTHOR: Mbalaviele G; Nishimura R; Myoi A; Niewolna M; Reddy S V; Chen D; Feng J; Roodman D; Mundy G R; **Yoneda T (Reprint)**
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, DEPT MED ENDOCRINOL, 7703 FLOYD CURL DR, SAN ANTONIO, TX 78284 (Reprint); UNIV TEXAS, HLTH

SCI CTR, DEPT MED, DIV ENDOCRINOL & METAB, SAN ANTONIO, TX 78284; UNIV TEXAS, HLTH SCI CTR, DIV HEMATOL, SAN ANTONIO, TX 78284; OSAKA UNIV, FAC DENT, DEPT BIOCHEM, OSAKA 565, JAPAN
COUNTRY OF AUTHOR: USA; JAPAN
SOURCE: JOURNAL OF CELL BIOLOGY, (15 JUN 1998) Vol. 141, No. 6, pp. 1467-1476.
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021.
ISSN: 0021-9525.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 25

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Osteoclasts** are multinucleated cells of hemopoietic origin that are responsible for **bone** resorption during physiological **bone** remodeling and in a variety of **bone** diseases. **Osteoclast** development requires direct heterotypic cell-cell interactions of the hemopoietic **osteoclast** precursors with the neighboring **osteoblast**/stromal cells, However, the molecular mechanisms underlying these heterotypic interactions are poorly understood. We isolated cadherin-6 isoform, denoted cadherin-6/2 from a cDNA library of human **osteoclast**-like cells. The isolated cadherin-6/2 is 3,423 bp in size consisting of an open reading frame of 2,115 bp, which encodes 705 amino acids. This isoform lacks 85 amino acids between positions 333 and 418 and contains 9 different amino acids in the extracellular domain compared with the previously described cadherin-6, The human **osteoclast**-like cells also expressed another isoform denoted cadherin-6/1 together with the cadherin-6, Introduction of cadherin-6/2 into L-cells that showed no cell-cell contact caused evident morphological changes accompanied with tight cell-cell association, indicating the cadherin-6/2 we isolated here is functional. Moreover, expression of dominant-negative or antisense cadherin-6/2 construct in **bone** marrow-derived mouse stromal ST2 cells, which express only cadherin-6/2, markedly impaired their ability to support **osteoclast** formation in a mouse coculture model of **osteoclastogenesis**. Our results suggest that cadherin-6 may be a contributory molecule to the heterotypic interactions between the hemopoietic **osteoclast** cell lineage and **osteoblast**/**bone** marrow stromal cells required for the **osteoclast** differentiation. Since both **osteoclasts** and **osteoblasts** /**bone** marrow stromal cells are the primary cells controlling physiological **bone** remodeling, expression of cadherin-6 isoforms in these two cell types of different origin suggests a critical role of these molecules in the relationship of **osteoclast** precursors and cells of **osteoblastic** lineage within the **bone** microenvironment.

L27 ANSWER 66 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 97:849676 SCISEARCH
THE GENUINE ARTICLE: YF254
TITLE: Biochemical characterization of the **binding** of echistatin to **integrin** alpha(v)beta(3) receptor
AUTHOR: Kumar C C (Reprint); Nie H M; Rogers C P; Malkowski M; Maxwell E; Catino J J; Armstrong L
CORPORATE SOURCE: SCHERING PLOUGH CORP, RES INST, DEPT TUMOR BIOL, 2015 GALLOPING HILL RD, KENILWORTH, NJ 07033 (Reprint)
COUNTRY OF AUTHOR: USA

Search completed by David Schreiber 308-4292

SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (NOV 1997) Vol. 283, No. 2, pp. 843-853.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0022-3565.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Echistatin is a 49-amino-acid **peptide** belonging to the family of disintegrins that are derived from snake venoms and are potent inhibitors of platelet aggregation and cell adhesion. Integrin alpha(v) beta(3) receptor plays a critical role in several physiological processes such as tumor-induced angiogenesis, tumor cell metastasis, osteoporosis and wound repair. In this study, we have characterized the binding of echistatin to purified integrin alpha(v) beta(3) receptor and the form expressed on human embryonic kidney 293 cells. We show that both purified and membrane-bound integrin alpha(v) beta(3) binds to echistatin with a high affinity, which can be competed efficiently by linear and cyclic **peptides** containing the RGD sequence. Previous studies have shown that alpha(v) beta(3) binds to vitronectin in a nondissociable manner, whereas an RGD-containing **peptide** derived from vitronectin binds in a dissociable manner with a K-d of 9.4 x 10(-7) M. Our studies indicate that radiolabeled echistatin binds to alpha(v) beta(3) in a nondissociable manner, similar to native echistatin. However, echistatin does not support the adhesion of 293 cells expressing alpha(v) beta(3) receptor because of poor binding to plastic dishes and is a potent antagonist of the adhesion of these cells to vitronectin. These studies demonstrate that echistatin binding to alpha(v) beta(3) is of high affinity and irreversible similar to vitronectin and provides an alternate ligand for high-throughput screening for alpha(v) beta(3) antagonists.

L27 ANSWER 67 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 97:684996 SCISEARCH
THE GENUINE ARTICLE: XP627
TITLE: Interactions of myeloma cells with **bone** marrow stromal cells via alpha 4 beta 1 **integrin**-VCAM-1 is required for the development of **osteolysis**.
AUTHOR: Michigami T (Reprint); Dallas S L; Mundy G R; **Yoneda T**
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, SAN ANTONIO, TX 78284
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (AUG 1997) Vol. 12, Supp. [1], pp. 104-104.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.
ISSN: 0884-0431.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L27 ANSWER 68 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 96:286941 SCISEARCH
THE GENUINE ARTICLE: UD853
TITLE: INHIBITION OF RETINAL-PIGMENT EPITHELIAL CELL-INDUCED TRACTIONAL RETINAL-DETACHMENT BY DISINTEGRINS, A GROUP OF ARG-GLY-ASP-CONTAINING **PEPTIDES** FROM VIPER VENOM

AUTHOR: YANG C H; HUANG T F; LIU K R; CHEN M S; HUNG P T (Reprint)
CORPORATE SOURCE: NATL TAIWAN UNIV HOSP, DEPT OPHTHALMOL, 7 CHUNG SHAN S RD, TAIPEI, TAIWAN (Reprint); NATL TAIWAN UNIV HOSP, DEPT OPHTHALMOL, TAIPEI, TAIWAN; NATL TAIWAN UNIV, COLL MED, INST PHARMACOL, TAIPEI 10764, TAIWAN
COUNTRY OF AUTHOR: TAIWAN
SOURCE: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (APR 1996) Vol. 37, No. 5, pp. 843-854.
ISSN: 0146-0404.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 51

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose. Integrin-mediated extracellular matrix (ECM) attachment plays an important role in vitreous contraction of retinal pigment epithelial (RPE) cells. Disintegrins, a group of Arg-Gly-Asp (RGD)containing **peptides** from viper venom, are potential anti-adhesion agents that interfere with **integrin**-ECM **binding**. This study was performed to determine whether disintegrins were effective in inhibiting RPE cell-induced matrix attachment in vitro and tractional retinal detachment in a rabbit model in vivo.

Methods. Two disintegrins, echistatin from viper Echis carinalus and flavoridin from Trimeresurus flavoviridis, were used. The expression of integrins on the surface of bovine and rabbit RPE cells was examined by indirect immunofluorescent stain with specific anti-integrin monoclonal antibodies. The inhibitory effect of disintegrins on RPE cell-mediated ECM attachment and vitreous contraction was evaluated with cell adhesion and vitreous contraction assays. In the in vivo model, rabbit eyes were injected intravitreously with either homologous rabbit RPE cells alone or together with disintegrins to induce tractional retinal detachment The cytotoxic effect of disintegrins was examined with a cell proliferation assay using the alamar blue method. Retinal toxicity of disintegrins was evaluated with electroretinograms and histologic examination of the rabbit eyes.

Results, Bovine and rabbit RPE cells showed the positive staining for the integrins alpha(2) beta(1) and alpha(5) beta(1) on cell surface. Disintegrins, echistatin, and flavoridin inhibited RPE cell attachment to the ECM. The potency of disintegrins was 150 to 300 times higher than that of Gly-Arg-Gly-Asp-Ser (GRGDS) **peptide**. The disintegrins also inhibited RPE cell-induced vitreous contraction in a dose-dependent manner, whereas the GRGDS **peptide** had no effect. In the in vivo experiment, echistatin (50 mu g/ml) or flavoridin (80 mu g/ml) significantly inhibited RPE cell-induced tractional retinal detachment compared with the control group at week 2 ($P < 0.05$) and week 4 ($P < 0.01$) after surgery. Disintegrins were nontoxic to RPE cells and rabbit retina as evaluated by cytotoxicity tests, electroretinograms, and histologic examinations.

Conclusions, The disintegrins were effective in inhibiting RPE cell attachment to the ECM and vitreous contraction in vitro. They also were effective in suppressing RPE cell-induced tractional retinal detachment in the rabbit eyes. They were nontoxic. Disintegrins and their analogs might be potential anti-adhesion therapeutic agents in the treatment of proliferative vitreoretinopathy.

L27 ANSWER 69 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 94:742595 SCISEARCH
THE GENUINE ARTICLE: PT481
TITLE: LIGAND AND CATION-BINDING ARE DUAL FUNCTIONS OF A DISCRETE

SEGMENT OF THE INTEGRIN BETA(3) SUBUNIT - CATION DISPLACEMENT IS INVOLVED IN LIGAND-BINDING

AUTHOR: DSOUZA S E (Reprint); HAAS T A; PIOTROWICZ R S; BYERSWARD V; MCGRATH D E; SOULE H R; CIERNIEWSKI C; PLOW E F; SMITH J W

CORPORATE SOURCE: CLEVELAND CLIN FDN, DEPT MOLEC CARDIOL, CTR THROMBOSIS & VASC RES, FF20, CLEVELAND, OH, 44195 (Reprint); SCRIPPS CLIN & RES INST, DEPT VASC BIOL, LA JOLLA, CA, 92037; CORVAS INT INC, SAN DIEGO, CA, 92121

COUNTRY OF AUTHOR: USA

SOURCE: CELL, (18 NOV 1994) Vol. 79, No. 4, pp. 659-667.
ISSN: 0092-8674.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: ENGLISH

REFERENCE COUNT: 55

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The alpha(IIb)beta(3) **integrin binds** Arg-Gly-Asp-containing (RGD-containing) ligands in a cation-dependent interaction. A fourteen amino acid sequence, beta(3)(118-131), and an antibody to it, inhibited ligand binding functions of alpha(IIb)beta s, and a 1:1 stoichiometric beta(3)(118-131)-RGD complex was detected by mass spectroscopy. Cation binding to Ps(118-131) was demonstrated by terbium luminescence and mass spectroscopy. Notably, ligand displaced cation from the beta(3)(118-131) **peptide** and also from purified alpha(IIb)beta(3). Thus, beta(3)(118-131), a highly conserved region in **integrin** beta subunits, **binds** both ligand and cation. Formation of a ternary complex between cation, ligand, and receptor, with subsequent displacement of cation from beta(3)(118-131)and a second site within the receptor, may be central to the mechanism of ligand recognition by integrins.

L27 ANSWER 70 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 94:658938 SCISEARCH

THE GENUINE ARTICLE: PK882

TITLE: RECOGNITION OF CRYPTIC SITES IN HUMAN AND MOUSE LAMININS BY RAT OSTEOCLASTS IS MEDIATED BY BETA-3 AND BETA-1 INTEGRINS

AUTHOR: HORTON M A (Reprint); SPRAGG J H; BODARY S C; HELFRICH M H

CORPORATE SOURCE: ST BARTHOLOMEWS HOSP, IMPERIAL CANC RES FUND, HAEMOPOIESIS GRP, LONDON, ENGLAND (Reprint); YAMANOUCHI RES INST, OXFORD, ENGLAND; GENENTECH INC, S SAN FRANCISCO, CA, 94080; UNIV ABERDEEN, DEPT MED & THERAPEUT, ABERDEEN, SCOTLAND

COUNTRY OF AUTHOR: ENGLAND; USA; SCOTLAND

SOURCE: BONE, (NOV/DEC 1994) Vol. 15, No. 6, pp. 639-646.
ISSN: 8756-3282.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE; CLIN

LANGUAGE: ENGLISH

REFERENCE COUNT: 68

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Laminins may be encountered by osteoclasts and their precursors in basement membranes when they migrate from periosteal vasculature during skeletal development and in pathological situations. We have examined the recognition by osteoclasts of intact laminins and their proteolytic derivatives, and analysed the mechanism of adhesion. Rat osteoclasts fail to bind intact mouse Engelbreth-Holm-Swarm (EHS) laminin (3% adhesion relative to adhesion to foetal calf serum proteins) and bind only weakly

to native human placental laminin (13%) or human merosin (9%). Pepsin treatment of native mouse EHS and human laminins in creased osteoclast adhesion. Rat osteoclasts adhered to mouse EHS laminin derived P1 fragment (70%), but failed to bind the E8 fragment, which contains adhesion sites recognised by some **integrins**. **Binding** to human and mouse P1 laminins was abolished by treatment with RGD-containing **peptides** and required divalent cations, but not by YIGSR **peptide**. Combinations of monoclonal antibodies to rat beta 3 and alpha v **integrins** reduced **binding** to P1 fragment by 91% and to human laminin by 72%, demonstrating that the major integrin involved in rat osteoclast adhesion to proteolysed laminin is alpha v beta 3. Antiserum to beta 1 integrin inhibited adhesion to human laminin by 40%, but to P1 fragment by only 8%; this suggests that pi integrin(s) contribute to osteoclast adhesion to human laminin but probably not to P1 fragment. The involvement of alpha v beta 3 integrin was confirmed using a recombinant human alpha v beta 3 solid phase binding assay. alpha v beta 3 bound to mouse P1 fragment and proteolytically digested human laminin, but not intact laminins. Binding of the alpha v beta 3 receptor to both laminins was significantly inhibited by RGD **peptides** and by monoclonal antibody 9C9 to human beta 3 integrin. In conclusion, our findings demonstrate that rat osteoclasts bind to laminin only when cryptic **peptide** sites become functional after exposure by proteolytic cleavage, and that both beta 3 and, to a lesser degree, beta 1 integrins are involved in this process.

L27 ANSWER 71 OF 71 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 93:615277 SCISEARCH
THE GENUINE ARTICLE: MA242
TITLE: MODULATION OF CALCITONIN **BINDING** BY **CALCIUM** - DIFFERENTIAL-EFFECTS OF DIVALENT-CATIONS
AUTHOR: STROOP S D (Reprint); MOORE E E; KUESTNER R E; THOMPSON D L
CORPORATE SOURCE: ZYMOGENET INC, 4225 ROOSEVELT WAY NE, SEATTLE, WA, 98105 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF RECEPTOR RESEARCH, (1993) Vol. 13, No. 8, pp. 1173-1197.
ISSN: 0197-5110.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 46

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Binding of salmon calcitonin to bovine hypothalamic membranes is enhanced about 25% by calcium with a half-maximal effect at 15 mM calcium. In contrast, membranes prepared from a cell line expressing a recombinant human calcitonin receptor show no effect of calcium under similar conditions. The hypothalamic calcitonin receptor solubilized with CHAPS detergent retains an apparent Kd of 0.3 nM for salmon calcitonin; however, binding of calcitonin to the detergent-solubilized receptor complex can be inhibited by divalent cations in order of potency Mn>Ca almost-equal-to Sr almost-equal-to Mg>>NaCl with Mn and Ca having apparent Ki's of 5 mM and 20 mM respectively. Dixon and Scatchard plots of Mn and Ca inhibition of binding to the soluble receptor complex suggest a noncompetitive mechanism of inhibition. **Calcium** also inhibits calcitonin **binding** to a detergent-solubilized recombinant human calcitonin receptor. Inhibition of calcitonin binding is observed using two independent methods for determining soluble receptor-hormone complex and inhibition is reversed by EDTA.

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These data suggest that a low-affinity divalent-cation binding site exists on the calcitonin receptor complex with a **binding** preference for **calcium** and manganese. **Binding** of **calcium** to this site can perturb the binding of calcitonin. This divalent-cation site may be an important structural component of the calcitonin receptor complex and have a potential physiological role in regions of high extracellular calcium such as at sites of **bone resorption**.